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CHAPTER 5

Hottest and Slowest Vials in an Endpoint-Aware Freeze-Drying Simulator

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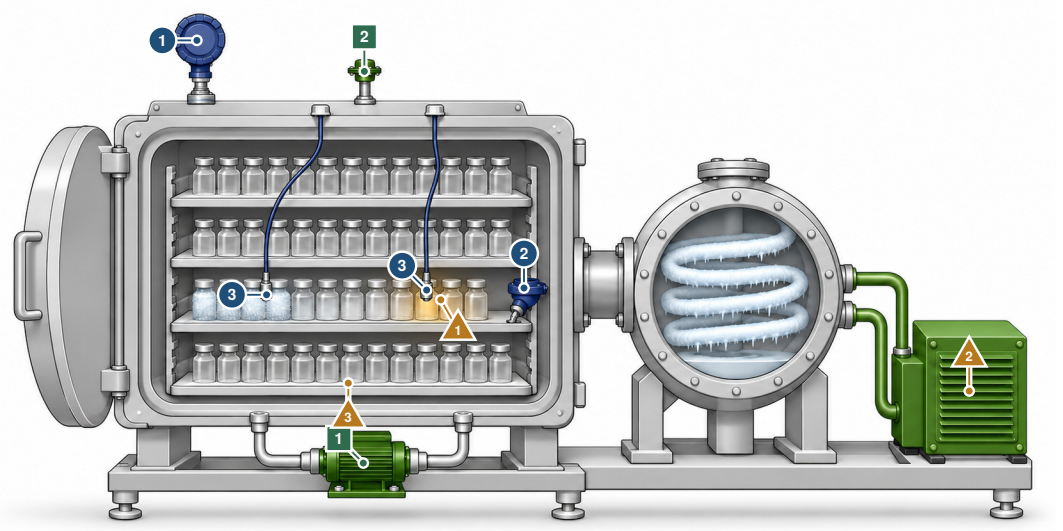
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CHAPTER 5

Hottest and Slowest Vials in an Endpoint-Aware Freeze-Drying Simulator



The controller moves 1 heating and cooling fluid for the shelves 2 nitrogen bleed that sets the chamber pressure

The controller reads 1 chamber pressure gauge 2 shelf temperature 3 two probes in sample vials

What disturbs it 1 vials that dry unevenly 2 condenser cooling falling short 3 poor contact under the vials

Vials on one shelf do not dry alike, so the warmest set how hot the shelf may run and the slowest set when drying may end. Illustration, not to scale.

IN PLAIN TERMS **Drying Medicine in Bottles Without Spoiling Any**

The main idea. Some medicines are frozen in small glass bottles. The ice then turns straight into vapor in a chamber pumped almost empty of air, while a warm shelf feeds in the heat.

The challenge. Bottles at the edge of the shelf get extra heat and can melt their dry cake, while bottles in the middle dry last. The sensors watch only two bottles and the gas, so the cycle must guard the hottest and wait for the slowest.

Why it matters. A cycle set for an average bottle spoils some bottles or wastes many hours.

THREE WAYS TO READ THIS CHAPTER

Explore	12 min	the first page, the history in Section 5.2, the fact in Section 5.3, the two try-its and the second fact in Section 5.6, and the key points
Study	55 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 5.6), Technology in Practice (Section 5.7), Limitations (Section 5.8) and the open challenges

The control question A shelf of identical vials does not dry alike: the outer edge runs warmest and the center dries last, while the instruments see two probed vials or the whole chamber. How should a freeze-drying cycle set the shelf, end primary drying and finish secondary drying so that both the hottest and the slowest vials pass?

Learning objectives

- Explain why the hottest group limits the shelf and the slowest group decides the endpoint, and size the heat difference from the K_v fits.
- Compute the vapor the duct carries and show when the chamber pressure is lost to the vapor.
- Compare a recipe clock, product probes and the Pirani comparison as endpoints of primary drying.
- Assess what an estimator with a learned resistance gains and what a wrong gauge law costs.
- Judge whether a predictive controller's gain comes from its horizon or from the pressure it is allowed to set.

Prerequisites Sections 1.4.1, 1.4.2, 1.4.4, 1.6.2 and 1.6.4. Section 1.6.3 for the predictive option only.

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See also Volume 5, Chapter 10 for moisture and a glass transition inferred from slow measurements, and Volume 5, Chapter 11 for a product temperature no instrument reaches. Volume 9, Chapter 4 for offset-free predictive control with a disturbance model.

5.1 Introduction

Freeze-drying removes the water from a frozen solution by subliming its ice under vacuum and then desorbing the water that never froze, and it leaves a porous cake that keeps a heat-sensitive medicine stable on the shelf. It is also slow. The standard operation of a batch freeze-dryer is protocol driven, with every phase programmed at fixed times and its process parameters held constant or interpolated between setpoints, which has been shown to be time consuming and inefficient [1]. In the pilot batch simulated here, 3066 vials each hold 3 mL of a 3 % sucrose solution, 8.90 kg of ice in all. A conservative recipe holds the shelf at −28 °C for 40 h of primary drying. The outer-edge vials are free of ice at 21.2 h and the center vials at 25.1 h, so the last 14.9 h of primary drying dry nothing, and the batch is stoppered at 50.0 h.

One belief is the target of the simulator, that a batch of identical vials on one shelf at one pressure behaves like one vial. The vial heat transfer coefficient has contributions from contact, conduction through the gas under the vial and radiation, and it depends on the chamber pressure and on the vial [2]. Vials at the front and side of an array sublime faster than those in the center because of atypical radiation from the surroundings [3]. At 10 Pa the fitted coefficient of an outer-edge vial is 24.2 W/(m^2 K) against 18.4 W/(m^2 K) for a center vial, 32 % more heat for the same shelf. The outer edge therefore limits how warm the shelf may run while the center decides when primary drying may end, and a recipe tuned on an average vial gets both decisions wrong. A transfer function from shelf to product temperature carries neither.

The class is general. A population of units in one batch, a limit set by its most exposed members and a completion set by its slowest, observed through a few sensors placed where someone could reach and through one slow aggregate signal, describes kiln and oven loads, battery formation, grain bins and other tray-loaded dryers. In Chapter 6 the coldest thermocouple sets the ramp of a composite cure while the hottest one sets its limit, and in Volume 5, Chapter 11 the temperature that decides the product is inside a brick that no instrument reaches. Freeze-drying makes the class concrete with published data. Product thermocouples sample a few vials, and the comparison of a Pirani gauge with a capacitance gauge has been found the best of several methods for detecting the end of primary drying [4]. Monitoring tools for product temperature, heat flux and sublimation flow have been reviewed for both laboratory and production scale [5], and model-based controllers for primary drying include in-line optimization of the heating fluid [6], model predictive control [7], a risk-based real-time strategy with model uncertainty [1] and multi-vial control validated on a pilot unit [8].

These studies report one dryer and one formulation at a time, and none lets a reader see the edge vials collapse while the center vials still hold ice, then change the policy, the endpoint and the secondary-drying plan and see which group fails. The simulator of this chapter is that experiment, a shelf-loaded batch of vials that keeps each group's true ice, front temperature and moisture apart from what its instruments and estimator report. It measures how a fixed recipe, probe-limited feedback and an endpoint-aware policy trade cycle time against the hottest and slowest groups. A fourth policy, model predictive control on the estimator's model, is measured against the same three, against the endpoint-aware policy retuned once by the controller's own tuning rule, and under 18 fault and mismatch conditions on two loads. The sublimation model, the vial heat transfer fits, the Pirani endpoint, the estimator, the shelf policies and the predictive controller follow the cited work. The measured results are specific to this model and calibration. Among them, an endpoint-aware policy stoppers the challenge batch 1.38 h sooner than a fixed recipe tuned on the same batch, but only 0.31 h of the gain comes from primary drying, and the same settings collapse every group when the Pirani law the estimator inverts is off by 6 %. What the predictive controller measurably adds is the chamber pressure handled without a rule, not cycle time.

The chapter runs as follows. Section 5.2 follows the domain from the first freeze-dried sera to model-based cycles. Section 5.3 sets out the batch as a five-group model whose ice and energy ledgers close to 1.2×10^{-14} relative over a whole cycle, with a quasi-steady chamber balance and the full equation set from which the simulator can be rebuilt. Section 5.4 gives the loops, the four shelf policies, the estimator, the endpoint rules and an ideal-information bound, with the predictive controller in Section 5.4.4. Section 5.5 separates code verification from agreement with the calibration study. Section 5.6 measures the nine cases and the challenge, the sensitivity to the batch and to the gauge law, and the predictive controller against the rule-based policies. Section 5.7 describes the gauges, the shelf fluid and the control system of a real dryer. Section 5.8 states the limitations, and the Exercises use the cases, each of which carries a completion rule (Section 1.6.4).

5.2 From Lyophile Serum to Model-Based Cycles

Drying biological material from the frozen state is older than its pharmaceutical use. An improved method of desiccation for biological problems was reported in 1909 [9], and in 1935 a procedure of rapid freezing and rapid dehydration from the frozen state, with the product vacuum sealed in the container in which it is stored and distributed, was described in detail for sera, antisera, enzymes and viruses, with apparatus for research laboratories, hospitals and industrial-scale production [10]. Drying in the final container, the arrangement the simulator models with vials, was part of the process from that start.

The physics of the vial came later. A 1984 study divided the resistance to vapor flow among the dried product, the semistoppered vial and the chamber, found the stopper and chamber resistances about a factor of ten below the dried product's, and described the heat reaching the vial through a heat transfer coefficient with three parallel mechanisms, each significant, whose values differ between vials of nominally the same specification while vials from one lot vary by about 4 % [2]. The product limit is a property of the formulation and of how it is measured. The collapse temperature in freeze-drying depends on the measurement methodology and on the rate of water removal from the glassy phase [11], and water plasticizes amorphous pharmaceutical solids in a way that a simplified Gordon–Taylor relationship describes [12], which is the law the simulator uses for the cake once its ice is gone.

Regulators wrote the practice down before the models were common, as the history segment below tells.

> ⧖ HISTORY **1993: An Inspection Guide Writes Down the Cycle**
>
> The United States inspection guide for freeze-dried injectables of 1993 set down what an inspector should expect of a cycle. After freezing and during primary drying, it is desirable to hold the product at least 4 to 5 degrees below its eutectic point. The dryer should control and record the shelf temperature, the product temperature, the condenser temperature, the chamber pressure and the condenser pressure, and the manufacturing directions should give time, temperature and pressure limits for the cycle. Cycles once run by cam-type recorder-controllers were giving way to microcomputer control, with the operator loading the chamber, placing probes in product vials and entering the cycle's parameters. The guide also recorded metal trays left under the vials that warped at one manufacturer and caused a moisture problem in some dosage units of a batch [13], the failure the simulator's poor-contact case represents.

The position effect was traced to its cause in 2003, when gold-coated vials and radiation shields showed that atypical radiation makes front and side vials sublime faster than center vials [3]. Feedback on the whole batch followed. Manometric temperature measurement coupled to an expert system set the shelf temperature, found drying end points and estimated residual moisture in a single laboratory run [14], and the Pirani-against-capacitance comparison was judged the best batch method of those tested for the end of primary drying, a cheap and steam-sterilizable instrument [4]. Model-based control arrived in the same decade, as in-line optimization of the heating fluid on a small industrial apparatus [6] and as model predictive control of primary drying [7]. A design space built from separately measured heat transfer coefficients and mass transfer resistances and checked by two runs [15], and a quality-by-design treatment of secondary drying that fitted Arrhenius desorption kinetics for a sucrose solution [16], carried the same models into cycle development. The current answer combines them. A risk-based strategy that propagates the uncertainty of the heat transfer and resistance fits controls the edge vials first and the center vials after, and starts secondary drying only when both the uncertainty analysis and the Pirani comparison indicate the end of primary drying [1], and multi-vial control has been validated experimentally on a pilot-scale unit [8]. The simulator's primary drying is calibrated on the first of these two.

5.3 The Batch as Modeled

The simulated dryer has four shelves, three loaded by default, each holding 1022 10R vials in a hexagonal pack, as shown in Figure 5.1. The shelves are heated and cooled by a fluid from a thermal unit, the chamber is held at its setpoint by bleeding nitrogen in, and the vapor leaves through a duct to a condenser coil and a vacuum pump. A shelf is resolved into three groups, 126 outer-edge vials that see the door and walls, 118 inner-edge vials in the second row and 778 center vials, and two more vials carry the product thermocouples. Each group is one representative vial multiplied by its count, so a batch is five vial models. Every case starts at a documented checkpoint at the end of freezing and runs through a 1 h vacuum hold, primary drying, an optional soak and secondary drying to stoppering. Freezing itself is not simulated.

The variables are classified in Table 5.1. The states are the ice $m_{i,j}$, bottom temperature $T_{b,j}$ and bound water X_j of each of the five groups, the shelf fluid temperature T_s, the condenser coil temperature T_{cd} and its ice m_{cd}, and the bleed valve position u_b, nineteen in all, plus ledgers that integrate the sublimed ice, the heat in, the sensible heat, the desorbed water, the water reaching the condenser and the thermal duties. Units are SI except temperatures, which the states carry in °C and every physical relation converts to kelvin.

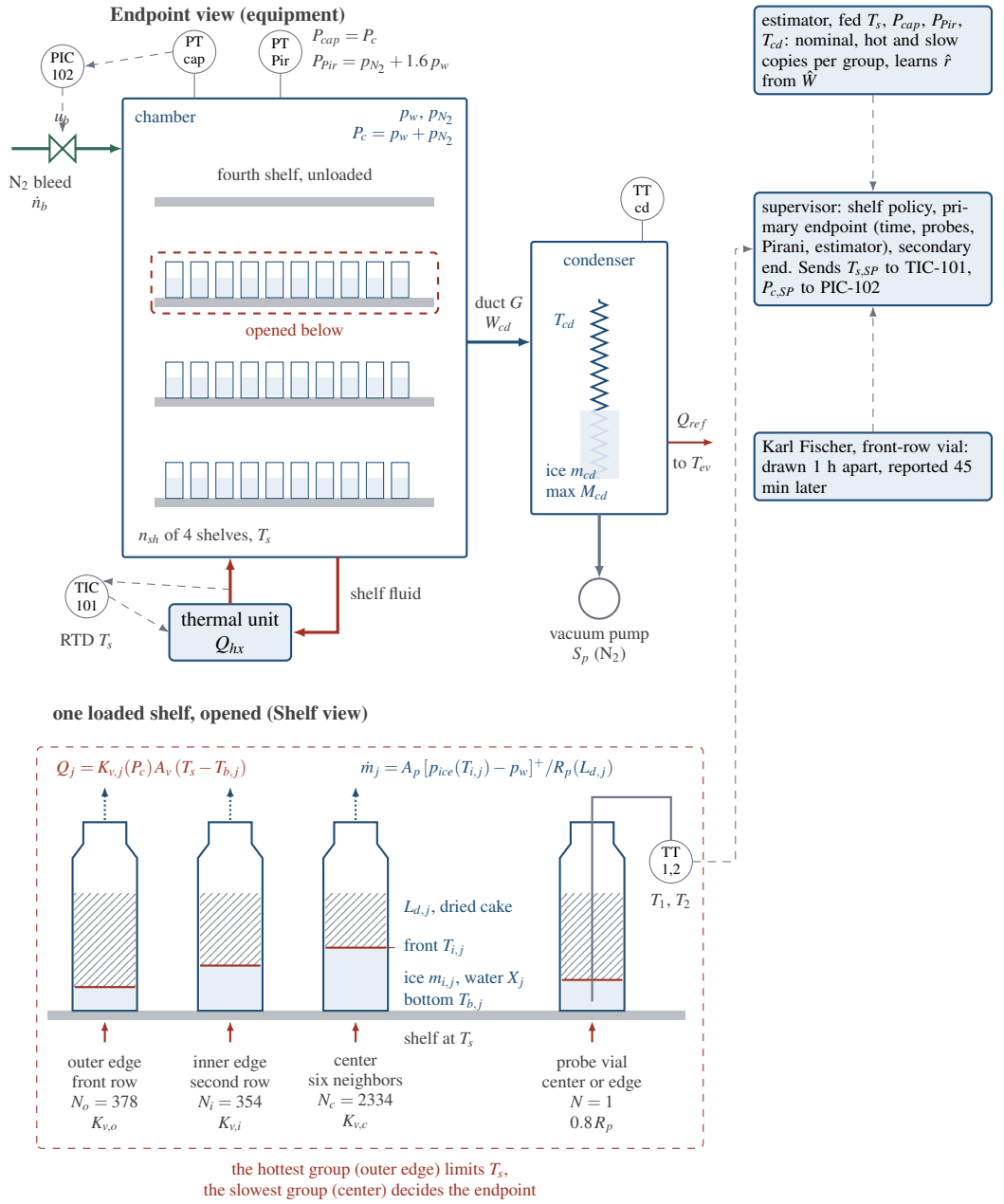


Figure 5.1 Freeze-dryer and vial groups as modeled. The chamber holds n_{sh} loaded shelves at T_s, water vapor p_w and nitrogen p_{N_2} from the bleed u_b under PIC-102, and the vapor crosses a duct of conductance G to the condenser coil at T_{cd} with ice m_{cd} and refrigeration Q_{ref}. One loaded shelf is opened below into its outer-edge, inner-edge and center groups and a probe vial, each with heat Q_j through $K_{v,j}$, a frozen layer $m_{i,j}$ below the front at $T_{i,j}$, a dried cake of thickness $L_{d,j}$ and a bottom at $T_{b,j}$. Heat flows are solid arrows, vapor dotted arrows and measurements dashed lines, and model states are labeled in blue. Process model only, not an equipment drawing. Not to scale.

Table 5.1 Roles of the Variables, With Checkpoint Values From Case 1

Variable	Role	Checkpoint	Range
T_s	CV of TIC-101 (RTD)	−40.0 °C	−55 to 50
P_c	CV of PIC-102 (capacitance)	10.0 Pa SP	5–30 Pa
$\max(T_1, T_2)$	CV of TIC-103 (probes)	−47.9 °C	—
Q_{hx}	MV, thermal-unit duty	−0.04 kW	−2.5 to 3.0 kW
u_b	MV, nitrogen bleed	20.6 %	0–100 %
$T_{s,SP}$	MV of the supervisor	−40.0 °C	ramp-limited
contact	DV, center K_v	100 %	60–110 %
r	DV, product resistance	100 %	60–160 %
b_T	DV, probe bias	0 K	±3 K
condenser	DV, refrigeration available	100 %	20–100 %
$m_{i,j}$	states, ice per vial	2.903 g	0–2.903
$T_{b,j}$	states, vial bottom	−47.2 to −47.9 °C	—
X_j	states, bound water	0.08 kg/kg	≥ 0
T_{cd}, m_{cd}	states, condenser	−75.6 °C, 0 kg	≤ 15 kg
p_w, p_{N_2}	algebraic, chamber	3.99, 6.01 Pa	—
$T_{i,j}$, $\dot{m}_j$	algebraic, front and flow	−48.3 °C (center)	—

5.3.1 Sublimation Through the Dried Layer

Ice at the front sublimes at a rate set by the difference between its vapor pressure and the chamber's water vapor, divided by the resistance of the dried layer above it, as shown in Equation (5.1).

$$\begin{aligned} \dot{m}_j &= \frac{A_p\,\varphi_j\left[p_{ice}(T_{i,j}) - p_w\right]^+}{R_{p,j}} \\ R_{p,j} &= r\,f_j\left(R_{p0} + \frac{A_{Rp}L_{d,j}}{1 + B_{Rp}L_{d,j}}\right) \\ L_{d,j} &= \frac{m_{i0} - m_{i,j}}{\rho_{ice}\,\varepsilon\,A_p}, \qquad \varphi_j = \sqrt{\min(1,\ m_{i,j}/m_{tail})} \\ \ln p_{ice} &= 9.550426 - \frac{5723.2658}{T} + 3.53068\ln T \\ &\quad - 0.00728332\,T \end{aligned} \tag{5.1}$$

where $\dot{m}_j$ is in kilograms per second per vial, $A_p = \pi r_i^2$ is the product area, R_p is area-normalized in Pa m^2 s/kg (which reduces to the m/s the source prints), r is the batch resistance disturbance and $f_j = 0.8$ for the two probe vials and 1 otherwise. The bracket is never negative, so no ice forms on the cake, and p_{ice} is in pascals with T in kelvin. The factor φ_j lets the last 1 % of the ice, $m_{tail} = 0.01\,m_{i0}$, leave from a shrinking area, so a vial warms before its last ice is gone and the ice reaches zero in finite time. The resistance rises from 1.51×10^4 at zero thickness to 1.043×10^5 Pa m^2 s/kg at the full 8.56 mm layer, which is why a fixed shelf runs the front warmer late in primary drying than early.

5.3.2 Heat Into the Vial

The shelf heats the vial bottom, the bottom sits above the front by the conduction drop through the remaining ice, and the vial's heat capacity is kept, as shown in Equation (5.2).

$$\begin{aligned} Q_j &= K_{v,j}(P_c)\,A_v\,(T_s - T_{b,j}), \qquad K_v = \alpha + \frac{\beta P_c}{1+\gamma P_c} \\ T_{i,j} &= T_{b,j} - \frac{Q_j L_{ice,j}}{\lambda_{ice} A_p}, \qquad L_{ice,j} = \frac{m_{i,j}}{\rho_{ice}\,\varepsilon\,A_p} \\ C_j \frac{\mathrm{d}T_{b,j}}{\mathrm{d}t} &= Q_j - \Delta h_{sub}\dot{m}_j - \Delta h_{des} r_{d,j} \\ \frac{\mathrm{d}m_{i,j}}{\mathrm{d}t} &= -\dot{m}_j \\ C_j &= m_{i,j}c_{ice} + m_s c_s + m_s X_j c_w + C_{gl} \end{aligned} \tag{5.2}$$

where $A_v = \pi r_o^2$, $c_w = 4180\,\mathrm{J/(kg\,K)}$ and $r_{d,j}$ is the desorption rate of Equation (5.4). The coefficients α, β and γ are fitted separately for center and edge vials in the calibration study. The inner edge sits 35 % of the way from center to edge, $K_{v,i} = K_{v,c} + 0.35(K_{v,o} - K_{v,c})$, a teaching interpolation, and the contact disturbance scales $K_{v,c}$ alone. The coefficient is gravimetric, so it already contains the radiation the edge vials receive and no separate radiation term is added. Because K_v depends on P_c, P_c on p_w and p_w on every front temperature, the three are solved by three fixed-point passes at every evaluation.

5.3.3 The Chamber, the Condenser and the Bleed

The chamber's water vapor holds about 0.4 s of flow against a 10 s step and hours of drying, so its balance is solved at quasi-steady state, as shown in Equation (5.3).

$$\begin{aligned} W_{cd} &= \sum_j N_j(\dot{m}_j + r_{d,j}) \\ &= \frac{M_w G\,\phi_{cd}}{R\,T_{gas}}\big(p_w - p_{ice}(T_{cd})\big) \\ p_{N_2} &= \frac{u_b\,\dot{n}_b\,R\,T_{gas}}{S_p}, \qquad P_c = p_w + p_{N_2} \\ C_{cd}\frac{\mathrm{d}T_{cd}}{\mathrm{d}t} &= \Delta h_{sub} W_{cd} + UA_{lk}(T_{wall} - T_{cd}) - Q_{ref} \\ Q_{ref} &= \mathrm{clip}\big(UA_{coil}(T_{cd} - T_{ev}),\ 0,\ Q_{ref,max}\big) \\ \frac{\mathrm{d}m_{cd}}{\mathrm{d}t} &= W_{cd}, \qquad \tau_v \frac{\mathrm{d}u_b}{\mathrm{d}t} = u_{b,cmd} - u_b \\ C_{sh}\frac{\mathrm{d}T_s}{\mathrm{d}t} &= Q_{hx} - \sum_j N_j Q_j + UA_w(T_{wall} - T_s) \end{aligned} \tag{5.3}$$

where N_j is the count of group j, $\phi_{cd} = \mathrm{clip}\big((1.1M_{cd} - m_{cd})/(0.2M_{cd}),\ 0.05,\ 1\big)$ narrows the vapor path as the coil approaches its ice capacity, and C_{sh} is 50 kJ/K per loaded shelf. The first line is linear in p_w for the groups whose front is warmer than the chamber vapor, so it is solved exactly with an active set that drops a group whose ice is colder. The bleed can only add gas, so when the vapor alone exceeds the setpoint the valve shuts and the vapor load, the duct and the coil decide the pressure. At 10 Pa of vapor with the coil at −73.2 °C the declared duct carries 0.654 kg/h, the equipment edge of case 3. The chamber pressure is not a free knob in this model.

> **+ DID YOU KNOW? A Speed Limit in the Duct**
>
> As the sublimation rate rises, the vapor flowing to the condenser approaches the speed of sound, about 350 m/s for water vapor at room temperature, and the flow then no longer depends on the pressure on the condenser side of the duct [17]. The simulator leaves this choked flow out and lets a declared duct conductance set its equipment edge.

5.3.4 Secondary Drying and the Moving Limit

Bound water desorbs from the share of the cake that is already dry, at a rate linear in its moisture with an Arrhenius constant, and the cake's glass transition follows the simplified Gordon–Taylor law, as shown in Equation (5.4).

$$\begin{aligned} \frac{\mathrm{d}X_j}{\mathrm{d}t} &= -k_d(T_{b,j})\,X_j\,f_{dry,j}, \qquad r_{d,j} = m_s k_d X_j f_{dry,j} \\ k_d &= k_{d,0}\,\mathrm{e}^{-E_{a,d}/(RT_{b,j})}, \qquad f_{dry,j} = 1 - m_{i,j}/m_{i0} \\ T_{g,j} &= \frac{w_j T_{g,w} + K(1-w_j)T_{g,s}}{w_j + K(1-w_j)}, \qquad w_j = \frac{X_j}{1+X_j} \end{aligned} \tag{5.4}$$

The kinetic and glass-transition constants were measured on 5 % sucrose in 2R vials [16], a different formulation and vial from the primary-drying calibration, and the bound water as the ice leaves, $X_0 = 0.08\,\mathrm{kg/kg}$ (a glass transition of 25.7 °C), is a teaching value. The same law sets the sticky point of milk powder in Volume 5, Chapter 10. At 25 °C the desorption time constant is 4.1 h and at 40 °C it is 2.0 h. Secondary drying therefore carries weaker evidence than primary drying, and every result that depends on it is read that way below.

5.3.5 The Score

Each group is judged on the truth at every step boundary. While more than its last 1 % of ice remains, its limit is the collapse temperature T_c at the front, and afterward it is the glass transition of its own cake at the vial bottom. The excursion $E_j = \int \max(0, T_j - T_{lim,j})\,dt$ is accumulated, and a group is scored collapsed above $E_{max} = 10\,\mathrm{K\,min}$, a scoring convention rather than a measured damage law. A collapsed cake is a defect whose potency the model does not quantify. The batch passes only if every group passes, no group holds ice at the ramp to secondary drying, and every group ends at or below 2 % moisture. The collapse limit is a path constraint and the moisture limit an endpoint constraint in the sense of Section 1.4.4. The cycle time with the worst group is the lead metric. Energy is reported as thermal duty (shelf heating, shelf cooling and condenser refrigeration), and an electricity figure counts the heater at 1, divides the cooling duties by declared coefficients of performance, 1.5 for the shelf chiller and 0.4 for the condenser, and adds a 1.5 kW pump for the whole cycle. That figure is an estimate built on teaching values, not a measurement.

5.3.6 Instruments

The controls read only a measurement packet. The shelf RTD lags 20 s with 0.05 K of noise, the capacitance gauge lags 2 s with 0.3 % relative noise and reads P_c, and the Pirani gauge, which is calibrated for nitrogen, reads $p_{N_2} + 1.6\,p_w$ through a 30 s lag with 0.5 % noise. The factor 1.6 is the source's ratio in a vapor-filled chamber, and the linear mixture law is a teaching form. Two thermocouples read the bottoms of the probe vials through 30 s lags with 0.1 K of noise plus the bias disturbance, and the condenser thermometer lags 30 s with 0.1 K. During secondary drying a sample thief pulls an outer-edge vial from the front row every hour, starting 15 min after the ramp, and the Karl Fischer result, with 0.06 points of noise, is reported 45 min after the pull and held until the next one. Every noise comes from one seeded generator.

Table 5.2 Parameters and Their Evidence. S Read in the Calibration Study (Primary Drying) or the Secondary-Drying Study, D Derived From S Values, T Teaching Value

Symbol	Meaning	Value	Unit	Ev.	Symbol	Meaning	Value	Unit	Ev.
r_i, r_o	vial radii, inner, outer	11.0, 12.0	mm	S	X_0, w_{max}	bound water, moisture limit	0.08, 2	kg/kg, %	T
V_{fill}, w_s	fill, sucrose (m/V)	3.0, 3	mL, %	S	E_{max}	collapse exposure	10	K min	T
ρ_{ice}, ε	ice density, porosity	919.4, 0.97	kg/m^3, –	S	c_{ice}, c_s, C_{gl}	heat capacities	1900, 1250, 2.4	J/(kg K), J/K	T
λ_{ice}	ice conductivity	2.45	W/(m K)	S	N_c, N_i, N_o	vials per shelf	778, 118, 126	—	T
Δh_{sub}	sublimation, 51 136.82 J/mol	2.839×10^6	J/kg	S, D	C_{sh}, UA_w	shelf and fluid, wall leak	50, 4	kJ/K, W/K	T
α_c, β_c, γ_c	center K_v fit	3.46, 1.93, 0.0292	K_v, K_v/Pa, 1/Pa	S	Q_{hx} limits	thermal unit	−2.5, +3.0	kW	T
α_e, β_e, γ_e	outer-edge K_v fit	−1.14, 4.46, 0.0757	same	S	G	duct conductance for vapor	2.5	m^3/s	T
f_{in}	inner edge between them	0.35	—	T	S_p, $\dot{n}_b$	pump (N_2), full bleed	0.05, 6×10^{-4}	m^3/s, mol/s	T
R_{p0}	resistance at zero layer	1.51×10^4	Pa m^2 s/kg	S	τ_v	bleed valve lag	20	s	T
A_{Rp}, B_{Rp}	resistance slope, curvature	9.68×10^7, 968	Pa m s/kg, m^{-1}	S	C_{cd}, UA_{coil}	coil, coil to refrigerant	60, 200	kJ/K, W/K	T
f_j	probed-vial resistance	0.80	—	T	T_{ev}, $Q_{ref,max}$	refrigerant, duty	−78, 1.2	°C, kW	T
T_c	collapse temperature	−34.25	°C	S	UA_{lk}, M_{cd}	coil leak, ice capacity	5, 15	W/K, kg	T
$k_{d,0}$, $E_{a,d}$	desorption, other formulation	277, 37 714	s^{-1}, J/mol	S	T_{wall}, T_{gas}	wall, gas for conversions	20, 293.15	°C, K	T
K, $T_{g,w}$, $T_{g,s}$	Gordon–Taylor	0.2721, 135, 347	–, K, K	S	Δh_{des}	heat of desorption	2.84×10^6	J/kg	T

5.3.7 Parameters, Checkpoint and Numerics

Table 5.2 gives the parameters with their evidence. The primary-drying coefficients are those of the calibration study [1], read in its Table 2, and everything about the dryer is a declared teaching value for a pilot machine. At the checkpoint the shelf is at −40 °C, every vial holds its full 2.903 g of ice (90 mg of sucrose and the bound water X_0 make up the rest of the fill), and a pseudo-transient finds the hold at which each vial takes as much heat as its sublimation needs, a center bottom of −47.7 °C with the bleed at 20.6 %, 3.99 Pa of vapor and 6.01 Pa of nitrogen. The ice and the ledgers are then put back full and zero. The engine of Section 1.6.1 integrates the states with a fixed 10 s step of fourth-order Runge-Kutta, the controls execute every 10 s and the historian logs a row a minute. Events (a group's last ice, a phase change, an assay draw) happen once at a step boundary, never inside the derivatives. A 50 h cycle takes 160 ms of computing headless and 50 s at the top speed of 3600 times real time in a browser.

5.3.8 Assumptions

Each group is one vial, so the scatter inside a group, which the source puts at 7.61 % in K_v and 1.10×10^4 Pa m^2 s/kg in R_p, is absent from the plant and appears only in the estimator's copies. A group whose peak is a few tenths of a kelvin under its limit would therefore still have vials over it. The front is flat, the conduction through the ice is quasi-steady and the shrinking-area tail is a declared form. Choked flow in the vial neck and the duct, stopper resistance, freezing, nucleation and ice-crystal size are outside the model, and a product-resistance slider stands in for their effect on R_p. The chamber is lumped and the vapor balance quasi-steady, which a test justifies by integrating the dynamic balance of a 1 m^3 chamber at 1 ms and finding it within 1×10^{-6} Pa of the algebraic value. The Pirani law is linear in the mixture. Secondary drying borrows its kinetics from another formulation. The collapse temperature, the exposure score and the moisture limit are teaching values, and real ones come from the product's specification and its regulator's assessment [13]. A simulated pass is not batch release.

5.4 Controllers, Estimator and Supervisor

Three PI loops run every $\Delta t_c = 10$ s on the velocity-form PID of Section 1.6.2, Equations (1.14) to (1.17), with the error $e = \mathrm{SP} - \mathrm{PV}$, no derivative action and a tracking time equal to τ_I. TIC-101 sets the thermal-unit duty from the RTD with $K_c = 400$ W/K and $\tau_I = 10$ min between −2.5 and 3.0 kW. PIC-102 sets the bleed from the capacitance gauge with 2 % per pascal and 120 s between 0 and 100 %, and it reports the pressure lost when its output is shut and the gauge still reads more than 0.5 Pa over the setpoint. TIC-103, in the probe-limited policy only, lowers the shelf setpoint so that the hotter probe stays at the limit less the margin, with 2 K of shelf per kelvin and 30 min, its output capped at the recipe's shelf target. The supervisor's shelf target reaches TIC-101 through a ramp limit

of 0.5 K/min upward in primary drying (the secondary ramp r_2 afterward) and 1 K/min downward, and it is held at the freezing temperature through the 1 h vacuum hold. In Manual the operator sets the duty and the bleed, and every loop tracks the applied output, so transfers are bumpless.

5.4.1 Three Rule-Based Shelf Policies

The fixed recipe ramps the shelf to its target and holds it. Probe-limited feedback is TIC-103. The endpoint-aware policy sets the shelf from an estimator, by the quasi-steady closed form that holds a vial's front at $T^* = T_{lim} - \Delta T_m$, as shown in Equation (5.5).

$$\begin{aligned} \hat{T}_s &= T^* + \hat{Q}\left(\frac{L_{ice}}{\lambda_{ice} A_p} + \frac{1}{\hat{K}_v A_v}\right) \\ \hat{Q} &= \Delta h_{sub} \frac{A_p \varphi \left[p_{ice}(T^*) - \hat{p}_w\right]^+}{\hat{R}_p} \end{aligned} \tag{5.5}$$

evaluated on the estimator's hot copy of the hottest group that still holds more than its last 1 % of ice. The target moves to the next group as each is predicted dry, never exceeds the recipe's shelf target, and, while the bleed command is below 3 %, eases down at 0.05 K/min instead of rising, because the vapor is then about to take the pressure. In secondary drying it is the lower of the secondary target and the estimated glass transition of the wettest cake less the margin. The policy is not a receding-horizon optimization and is not called model predictive control.

5.4.2 The Estimator and Its Learned Resistance

For each of the three batch groups the estimator integrates Equations (5.1), (5.2) and (5.4) with the calibration's constants, driven only by the RTD, the capacitance gauge and the vapor inferred from the two gauges, $\hat{p}_w = (P_{Pir} - P_{cap})/0.6$. It runs three copies per group, nominal, hot (K_v and R_p one standard deviation high) and slow (K_v low, R_p high), with the source's spreads of 7.61 % and 1.10×10^4 Pa m^2 s/kg. The gauges and the condenser thermometer also measure the batch's sublimation through the declared duct, and with learning on a common resistance multiplier follows the ratio of the estimator's own batch sublimation $\hat{W}_p$ to it, as shown in Equation (5.6).

$$\begin{aligned} \hat{W} &= \frac{M_w G}{R T_{gas}} \left(\hat{p}_w - p_{ice}(T_{cd,m})\right)^+ \\ \hat{r}_k &= \mathrm{clip}\left(\hat{r}_{k-1} \left(\hat{W}_p / \hat{W}\right)^a,\ 0.5,\ 2\right) \\ a &= 1 - \mathrm{e}^{-\Delta t_c / \tau_r}, \qquad \tau_r = 1\,\mathrm{h} \end{aligned} \tag{5.6}$$

The update runs in primary drying only, while every nominal copy holds more than 15 % of its ice. One flow cannot separate a resistance error from a heat transfer error, so a batch that takes less heat is read as a more resistant one, the safe direction. On batches that resist 85, 100, 115, 130 and 145 % of the calibration, the multiplier settles at 0.855, 0.997, 1.143, 1.295 and 1.445.

5.4.3 Endpoints and the Ideal-Information Bound

Primary drying ends on one of four rules: a recipe time, both probes within 2 K of the shelf for 30 min, a Pirani-to-capacitance ratio at or below 1.07 for 15 min after the first hour (the source's criterion [1]), or that ratio together with every slow copy dry. Secondary drying ends on a recipe time from the ramp, an assay at or below the moisture limit, or the estimator's wettest cake at or below it after 30 min. These are the clock, measured-event and estimate guards of Section 1.4.2. The ramp leaves the ice untouched, so leftover ice keeps subliming into a warming shelf. Every policy reads the same packet. An ideal-information bound reads the teaching truth instead, sets the shelf for each group's true front by Equation (5.5) with the true K_v, R_p and p_w, ramps at the first scan with no ice left, holds secondary drying under the true lowest glass transition less its margin and stoppers when

the true moisture passes. It runs through the same loops and ramp limits. It is a bound, not a policy a plant could run.

Three models are kept apart. The plant is Section 5.3. The identified models are the calibration study's K_v and R_p fits. The controller's model is the estimator's copy of those fits with one learned multiplier, the declared duct conductance and the linear Pirani law, which knows neither a contact loss nor the batch's true resistance. The predictive controller of Section 5.4.4 plans on that same estimator model and reads nothing else of the plant.

5.4.4 A Predictive Controller for Primary Drying

The fourth shelf policy is a receding-horizon quadratic program in the standard form [18], a structure long established in industrial practice [19] and already applied to primary drying [7], set up as the option of Section 1.6.3 describes in general. It acts in primary drying while TIC-101 and PIC-102 are both automatic. Every 10 min, which is 60 control scans with the first on the priming call at $t = 0$, it plans two setpoints and applies the first move. The shelf target u_T still passes through the shipped ramp limit and vacuum hold to TIC-101, and the pressure setpoint u_P reaches PIC-102 through a 0.25 Pa/min slew. Secondary drying under this policy follows the endpoint-aware rule, and the endpoint stays the estimator's.

The controller's model is the estimator's, made quasi-steady in the product temperature, as shown in Equation (5.7).

$$
\begin{aligned}
T_s &= T_{i,q} + Q_q\Big(\frac{L_{ice,q}}{\lambda_{ice}A_p} + \frac{1}{(1+z_q\sigma_K)K_{v,j}A_v}\Big)\\
Q_q &= \Delta h_{sub}\,\frac{A_p\varphi_q\big[p_{ice}(T_{i,q}) - p_w\big]^+}{\max(\hat{r},1)R_p(L_{d,q}) + z'_q\sigma_R}\\
p_w &= p_{ice}(T_{cd,m}) + b + \frac{RT_{gas}}{M_wG}\sum_j N_j\dot{m}_j^{nom}\\
C_{sh}\frac{\mathrm{d}T_s}{\mathrm{d}t} &= K_c(u_T - T_s) + z_I - \sum_j N_jQ_j^{nom}\\
&\quad + UA_w(T_{wall} - T_s)\\
\frac{\mathrm{d}z_I}{\mathrm{d}t} &= \frac{K_c}{\tau_I}(u_T - T_s), \qquad \tau_P\frac{\mathrm{d}P_c}{\mathrm{d}t} = u_P + \hat{d}_P - P_c
\end{aligned}
\tag{5.7}
$$

where q runs over nine vial copies, the hot, nominal and slow copy of each group j with (z_q, z'_q) equal to $(1,1)$, $(0,0)$ and $(-1,1)$, $\sigma_K = 7.61\,\%$ and $\sigma_R = 1.10\times10^4$ Pa m^2 s/kg. Every constant is the platform's declared value, frozen when the program loads. The first line is Equation (5.5) solved for the front, by a safeguarded Newton iteration to 1×10^{-10} K, so a copy's only state is its ice. The vapor closes through the declared duct from the measured coil temperature $T_{cd,m}$, and the bias b aligns it with the gauges' $\hat{p}_w$, moving halfway to the new difference at each decision. The shelf is TIC-101's PI without its clamp, on $C_{sh} = 50$ kJ/K per loaded shelf, and the pressure follows its setpoint with $\tau_P = \tau_{I,P}/(K_{c,P}K_G) = 205$ s, where $K_G = \dot{n}_bRT_{gas}/S_p = 29.25$ Pa per unit of bleed opening. The input disturbance $\hat{d}_P$ is the capacitance gauge's persisting offset from that lag, filtered over one decision, so a stuck bleed appears in it within minutes. With b and $\hat{d}_P$ the plan is offset-free on the two gauges in the disturbance-model sense [20]. A disturbance model is also how the estimator of Volume 9, Chapter 4 carries a fuel bias that no instrument measures. The batch's product temperature has no measurement, and the probes are not read. The plan takes the learned multiplier only in the careful direction, $\max(\hat{r},1)$, because one flow cannot distinguish a cake that resists less from a duct that carries less than declared (Section 5.6.9).

Step tests on case 4's batch at 8 h, each run minus an unstepped run on the same seed, check the loop models. For shelf-target steps of ±1 and $+3$ K the plant reaches 63 % in 300 to 460 s and the model in 320 to 480 s, a residual of 0.86 to 0.91 % RMS of the step. For pressure steps the plant takes

150 s and the lag 220 s, 3.6 % RMS, because the lag omits the PI's proportional feedthrough (with it, 2.4 %), a difference inside one decision. The quasi-steady front drops the vial's heat capacity, so the plan adds the estimator's dynamic front minus its own as a correction ℓ_q that decays with the copy's time constant τ_q, below 1 K and 3 to 4 min. One decision ahead, the plan's warmest judged front differs from the estimator's front 10 min later by 0.220 K RMS on case 9 (118 decisions) and 0.295 K on the challenge, at worst 2.2 K at the instant the judged copy passes to the next vial.

The horizon runs in steps of $\Delta = 10$ min from now to the predicted end of primary drying, the step at which every slow copy is dry under the previous plan, at most $N = 150$ steps (25 h), and it is re-evaluated at every decision. Twelve move blocks of geometrically growing length are spread over the N steps, and below two steps the previous plan is held. The nominal trajectory is the nonlinear model under the previous plan shifted by one decision, integrated by Heun's rule with the loops' exact zero-order hold, and the program of Equation (5.8) corrects it.

$$
\begin{aligned}
\min\ & -w_W \sum_{k=1}^{N} \delta W_k + \sum_{b=1}^{12} \left(S_T \Delta u_{T,b}^2 + S_P \Delta u_{P,b}^2 \right) \\
& + \sum_{\ell} \left(\rho\, \varepsilon_\ell^2 + \sigma \varepsilon_\ell \right) \\
\text{s.t. } & \bar{T}_{i,q,k} + s_{q,k} \left(\delta T_{s,k} + \gamma_q\, \delta P_{c,k} \right) \\
& \quad + \ell_q \mathrm{e}^{-k\Delta/\tau_q} \le T^* + \varepsilon_{q,k} \\
& \bar{h}_k + \delta h_k \le -1\,\mathrm{Pa} + \varepsilon_{h,k}, \qquad h = p_w - P_c \\
& T_{s,min} \le u_T \le T_{s,1}, \qquad |\Delta u_{T,b}| \le r_1 \Delta \\
& |u_P - P_{c,SP}| \le 5\,\mathrm{Pa}, \qquad |\Delta u_{P,b}| \le 2.5\,\mathrm{Pa}
\end{aligned}
\tag{5.8}
$$

The bar marks the nominal trajectory. The deviations δT_s and δP_c follow from the moves through the three linear loop states of Equation (5.7) discretized exactly over Δ, $s_{q,k}$ is the front's sensitivity to the shelf at step k along the nominal, γ_q the ratio of its pressure to shelf sensitivity at the first step, and δW_k the batch sublimation's linearized change in kg/h. The front row applies to one copy per group, the warmest of those still holding more than their last 1 % of ice (hot, then nominal, then slow), and when no copy is icy the shelf is held at its setpoint, as the shipped policy holds it. The vapor row stands for the condenser's capacity at the planned pressure, because the bleed loses the pressure once the vapor alone reaches it. The weights are $w_W = 10$ per kg/h, $S_T = 0.05$ per K^2, $S_P = 0.05$ per Pa^2, $\rho = 10^4$ and $\sigma = 10^3$ per kelvin or pascal. Both output rows are soft, with one slack per step over the first hour and one per row beyond, a weighting that keeps the plan from paying once for a violation and riding the limit afterward [21]. The input bounds are hard: $T_{s,min} = -55\,^\circ$C, $T_{s,1}$ the primary shelf ceiling, the shelf held through the vacuum hold, u_P within 5 to 30 Pa, and per block boundary one decision of the 0.5 K/min ramp ($r_1\Delta = 5$ K) and 2.5 Pa. The pressure box of ± 5 Pa about the recipe's setpoint $P_{c,SP}$ is a design choice. A higher pressure costs nothing in this model but the Pirani's contrast, so an open box drives the plan to 30 Pa, and the box keeps the recipe's pressure a meaningful setting. The program has 24 move variables and at most 34 slacks and is solved by the series' shared active-set solver.

The plan stands only when the solver returns an optimum, the move, plan, predictions, objective and slacks are finite, every slack is non-negative, every planned input lies in its box and the first planned move equals the applied one. Otherwise the historian is marked, the shelf passes to the endpoint-aware target and the pressure to the recipe through their ramps, and the next valid plan takes control back. A test that injects ten faults rejects all ten, and a forced fallback at 4.00 h moves the shelf by at most one scan of its ramp and the pressure by one scan of its slew. The shipped protections remain above the plan, namely the ramp limit, the vacuum and fluid-excursion holds, the endpoint rules, the pressure-lost check and the endpoint-aware bleed rule. The plan moves setpoints only, so no PI is switched and no transfer needs tracking. Its input is a packet of the instruments, the estimator's nine copies and $\hat{r}$, its own setpoints and the load configuration. A source scan catches 26

Table 5.3 Code Verification and Agreement With the Calibration Study

Check	Result
Code verification	
Ice and energy per group over three whole cycles (case 1, case 7 and the challenge): $m_{i0} - m_i = \int \dot{m}\,dt$ and $\int Q\,dt = \Delta h_{sub} \int \dot{m} + \Delta h_{des} \int r_d + \int C\,dT_b$	$\leq 8.4 \times 10^{-15}$ relative
Chamber and batch water ledgers, same cycles	$\leq 1.2 \times 10^{-14}$ relative
Batch water by an independent sum, challenge as shipped	5.4×10^{-7}, the logged clip of 7.5×10^{-9} kg per vial
R_p monotone in L_d, never falls in a run, heating never creates ice	0 falls, 0 increases
Design point by hand, case 4 at 12 h	$\dot{m}$ within 2.1×10^{-5}, $\Delta h_{sub}\dot{m}/Q$ 0.999–1.000
Step 10 to 5 s, the nine original cases and the suggested challenge	cycle ≤ 0.0014 h, peaks ≤ 0.010 K, 0 verdict flips
Seeds 1 and 2 against the default, same runs	≤ 0.028 h, ≤ 0.036 K, 0 flips
Suggested challenge played in 1 min and 1 h chunks	identical
Each case loaded first, from the list and after Reset	identical, 10 of 10
Agreement with the calibration study [1]	
Edge vial dry at a fixed 1.5 K margin, 10 Pa of vapor	18.1 h against 17.9 h
Center vial dry, same policy	21.9 h against 21.5 h
The same at a 1.0 K margin	16.4 and 19.9 h
Pirani ratio while subliming, case 1, 3 to 20 h	mean 1.34 against about 1.6

of 26 doctored copies that read the plant, a replay reproduces 36 decisions bit for bit from packets recorded on a plant with 140 % resistance, 75 % contact and an 80 % duct, and a collapse temperature the controls are not told leaves 48 decisions bit-identical.

The weights come from a rule fixed before any run. On case 9 alone, the grid $w_W \in \{1, 10, 100\}$ by $S_T = S_P \in \{0.005, 0.05, 0.5\}$ is searched for the shortest primary drying that keeps every group 0.25 K under its limit at every instant (scored on the truth after the run), never loses the pressure for more than 10 min and never falls back, with ties inside 0.05 h broken by the least shelf travel. All nine settings qualify, and $w_W = 10$ with $S = 0.05$ gives 21.16 h and 31 K. A decision costs 4.2 to 6.7 ms on average headless and 5.12 ms on average in a browser (10.5 ms at the 95th percentile, 24.1 ms at worst), measured with other jobs loading the host. At 3600 times real time the engine's stepping takes 4.40 % of the wall clock under the plan against 0.82 % under the endpoint-aware policy, at 60 frames per second. Because a decision exceeds 2 ms, a frame guard ends a frame's stepping after 25 ms, which drops wall time and never a step and held no frame.

5.5 Verification and Calibration

Code verification and agreement with the literature are reported apart in Table 5.3. The first half shows that the program solves the stated equations. The second compares the model with the study whose coefficients it uses, so it is a consistency check of the calibration, not an independent validation, and the heat transfer and resistance fits come from the same equipment as the drying times compared.

The source's 17.9 and 21.5 h come from a risk-based optimizer that sampled 10 000 vials and held the predicted front at the collapse temperature with a 0.1 % risk of failure. The 17.9 h is when its uncertainty analysis had all edge vials dry, and the 21.5 h (21.48 to 21.55 h over three normal runs) is when 99.9 % of its vials were dry [1]. The simulator compares nominal vials under a fixed margin instead. The 1.5 K is a derived stand-in, because 3.09 standard deviations of the front temperature, propagated from the source's own K_v and R_p spreads, run from 1.2 to 2.3 K over the drying of the two groups. The model's times are 1.2 % and 2.0 % longer than the source's. The Pirani ratio is a disagreement. The source reads about 1.6 in a chamber filled with water vapor, while the model's declared duct leaves nitrogen in the chamber, a mean ratio of 1.34 in case 1, which rises to 1.57 under the heavier sublimation of case 2 at 12.5 h. Secondary drying has no comparison of its own, because its constants come from another formulation.

Two logging defects at $t = 0$ were corrected when the predictive controller was added. The Pirani-to-capacitance ratio was blank on the first logged row of every run although both gauges read (it now logs 1.239 on case 1, 1.281 on case 9 and 1.236 on the challenge), and each group's peak over

Table 5.4 The Ten Cases

#	Case and settings	Teaching point
1	Recipe −28 °C, 40 h, then 25 °C for 10 h	the idle hours of a clock
2	Shelf −16 °C, Pirani endpoint	the edges collapse first
3	Four shelves at −18 °C, 18 h target	the vapor takes the pressure
4	Shelf −22 °C, Pirani endpoint	hottest is not slowest
5	Case 4, 20 h clock, center contact 80 %	a recipe time outgrown
6	Probe-limited, probes in the center, shelf up to 0 °C	the probes protect themselves
7	Case 4, front-row probes end primary drying	a premature endpoint
8	Case 4, 4 h of secondary drying at 25 °C	moisture against glass transition
9	Four shelves, predictive controller, shelf up to 0 °C, Pirani endpoint	shelf and pressure planned together
10	Challenge: 115 % resistance, bleed stuck at 45 % for 1 h at 5 h	a shorter cycle every group survives

Table 5.5 Measured Outcomes. Dry Hours Are Outer, Inner and Center Groups, Excursions Are Peak and Exposure Over the Limit

#	Configuration	Outcome
1	as shipped	dry 21.2, 23.6, 25.1 h, closest 3.7 K under, stoppered 50.0 h
	Pirani endpoint	ramp 25.4 h, stoppered 35.4 h
2	−16 °C	outer +1.2 K, 367 K min, inner +0.3 K, 40 K min, center 0.2 K under, primary 16.2 h
	−20 °C, −22 °C	0.3 and 1.1 K under, primary 18.4 and 19.8 h
3	as shipped	pressure lost 737 min, peak 14.1 Pa, outer +1.6 K, 693 K min, inner 267 K min, center 77 K min
	−24 °C	pressure held, intact, primary 22.5 h
	sweep, 115 runs each	four shelves 0 feasible (best 19.1 h), three 8 (best 17.2 h)
4	as shipped	dry 16.4, 18.3, 19.6 h, outer 1.1 K under, center 2.3 K under
5	as shipped	center dry 21.6 h, 10.7 % of its ice at the 20 h ramp, +2.0 K, 30 K min
	Pirani endpoint	ramp 22.6 h, stoppered intact 32.6 h
6	as shipped	outer +2.4 K, 416 K min, inner +1.6 K, center +1.1 K, pressure lost 84 min
	one probe on the edge, 2 K	outer +0.5 K, 4 K min, primary 23.7 h
	endpoint-aware	primary 19.6 h, every group ≥ 0.9 K under
7	as shipped	probe vials dry 15.4 h, ramp 16.0 h with 18.6 % of the center's ice, center +7.2 K, 286 K min
	Pirani endpoint	ramp 19.8 h, stoppered intact 29.8 h
8	as shipped	center 4.55 % moisture at stoppering
	6 or 8 h at 25 °C	2.83 or 1.75 %
	6 h at 35 °C	1.95 %, stoppered 25.8 h
	estimate, assay end	27.4 and 28.8 h, 1.95 and 1.38 %
	1 K/min to 40 °C	every group over its glass transition, center +7.6 K
9	as shipped	primary 21.16 h, pressure held, every group ≥ 1.26 K under (Table 5.9)

its limit logged 0 K where the opening state is 12.8 to 14.7 K under. Every later row of all 60 runs checked (ten cases, six settings each) is bit-identical, and no number in this chapter moved. Four other columns stay blank by design, the probe margins after primary drying, when their collapse limit no longer applies, and the assay columns before the first report.

5.6 Ten Cases, Measured

The cases appear in Table 5.4, and the app lists them as its numbered scenarios (Section 1.6.4). All start from the pilot cycle (three shelves, −40 °C at the checkpoint, a 1 h hold, 10 Pa, a 0.5 K/min ramp to the primary shelf, the fixed-recipe policy, a 1 K margin and probes in the center) and depart only as their rows say. The numbers below come from the headless engine at the default seed, advanced step by step exactly like the browser, and a setting a row lists is entered before Run. Peak excursions are on the truth, positive above the limit. Table 5.5 collects the outcomes.

5.6.1 One Shelf, Three Groups

Under the fixed −22 °C shelf of case 4 the outer edge is dry at 16.4 h and the center at 19.6 h, 3.2 h apart, and the outer edge comes within 1.1 K of the limit while the center stays 2.3 K under, as

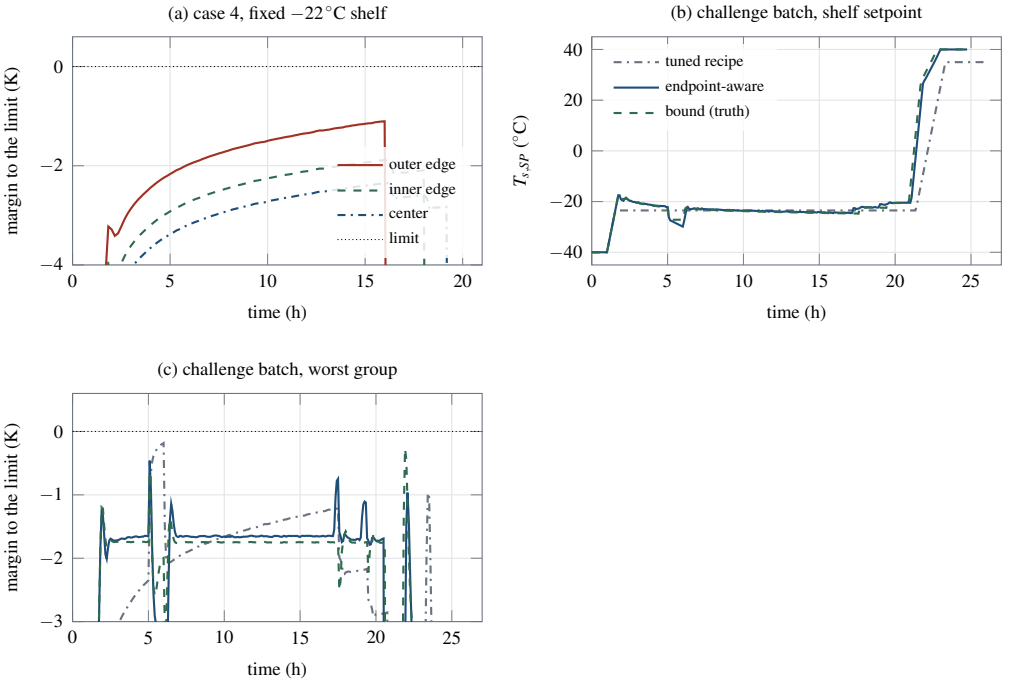


Figure 5.2 Mechanism and policy comparison from the simulator. (a) Case 4 as shipped, each group's margin to its limit (teaching truth: outer edge solid, inner edge dashed, center dash-dotted), each line leaving the plot when its group reaches its last 1 % of ice and its limit becomes the cake's glass transition. (b) The challenge batch under the strict tuned recipe (dash-dotted), the endpoint-aware settings (solid) and the ideal-information bound (dashed), shelf setpoint over the whole cycle. (c) The same three runs, the worst group's margin to its limit, the collapse temperature in primary drying and the glass transition after. Default seed, logged every 5 min in (b, c) and 10 min in (a).

shown in Figure 5.2a. The extra heat of the edge mostly goes into sublimation, but not all of it. Each margin shrinks as the dried layer thickens, the outer edge's from 2.44 K at 4 h to 1.15 K at 15 h, so a fixed shelf is set by the hottest group at the end of its drying. In case 2 the shelf at −16 °C drives the outer edge 1.2 K over the limit for 367 K min and the inner edge 0.3 K over for 40 K min, both collapsed, while the center peaks 0.2 K under. At 12.5 h the three groups stand on one screen, as shown in Figure 5.4. Two hours of primary drying (16.2 h against 18.4 h at −20 °C) buy the edges their structure.

> **TRY IT IN THE APP** **2 · Excess Shelf Heat**
>
> Load the scenario and press Run. Watch the three group cards beside the shelf map. The outer edge goes 1.2 K over its limit and the inner edge 0.3 K over, and both collapse, while the center peaks 0.2 K under. Primary drying ends at 16.2 h, two hours sooner than with the shelf at −20 °C.

Pause. Try Exercise 5.1 before reading on.

5.6.2 The Equipment Edge

Four shelves at −18 °C in case 3 make more vapor than the duct passes at 10 Pa. The bleed shuts, the pressure is lost for 737 min and peaks at 14.1 Pa, K_v rises with it, and all three groups collapse while the coil stays at −72 °C at its warmest, so the limit is the vapor path rather than the refrigeration. The

schedule's 18 h target for primary drying is infeasible on arithmetic alone. The declared duct carries 0.654 kg/h at 10 Pa of vapor, and four shelves hold 11.87 kg of ice, which is 18.1 h even if every vial sublimed at that rate from the first minute. A logged sweep of 115 four-shelf runs over every shelf policy, shelf targets of −26 °C to −16 °C, margins, ramps and pressures of 6 to 15 Pa finds none that ends primary drying by 18 h with the pressure held and every group intact (the best takes 19.1 h), while 8 of 115 three-shelf runs do. The case would not be run this way on a production dryer, but it serves to show a target that no controller can meet.

Pause. Try Exercise 5.2 before reading on.

OPEN CHALLENGE **Knowing What the Dryer Can Carry**

Every freeze-dryer supports a maximum sublimation rate at each pressure, set by its refrigeration capacity, its condenser area, the highest shelf temperature it reaches and choked flow, and the industry lacks a quantitative understanding of this equipment capability. Ice slab tests or laser absorption in the duct find the choke point, and turning the duct itself into a mass flow meter with computational fluid dynamics was an active project. Whether the critical pressure ratio can be calculated for a condenser placed below the chamber remained a research question [17]. Progress would be a capability curve known for every production dryer.

5.6.3 Measurements That Answer for Two Vials

In case 6 the probe loop holds both center probes near the limit less the margin, and every unprobed vial runs warmer than they do, because a probed vial here has 80 % of a normal vial's resistance (the direction reported for probed vials [15], the size a teaching value). All three groups collapse and the shelf drives hard enough early to lose the pressure for 84 min. One probe moved to the edge with a 2 K margin brings the outer edge to 0.5 K over for 4 K min, under the collapse score, at a primary drying of 23.7 h instead of 16.6 h, while the endpoint-aware policy, which reads no probe, ends it at 19.6 h with every group at least 0.9 K under. In case 7 the front-row probe vials are dry at 15.4 h and the probe rule ramps at 16.0 h with 18.6 % of the center's ice and 12.4 % of the inner edge's, which collapse at 7.2 K and 5.5 K over their limit. The Pirani endpoint ramps at 19.8 h, a quarter of an hour after the last center ice, and stoppers every group intact at 29.8 h. In case 5 a recipe clock written with half an hour to spare ramps at 20 h with 10.7 % of the center's ice still there, because the center takes 80 % of its heat. The Pirani does not need to know the contact, and it ramps at 22.6 h.

TRY IT IN THE APP **7 · A Premature Primary-Drying Endpoint**

Load the scenario and press Run. The front-row probe vials are dry at 15.4 h, the probe rule ramps at 16.0 h with 18.6 % of the center's ice left, and the center collapses 7.2 K over its limit. Press Reset, set End primary drying when to Pirani meets capacitance and run again: the ramp waits until 19.8 h, and every group is stoppered intact at 29.8 h.

5.6.4 Secondary Drying

Four hours at 25 °C in case 8 leave the center at 4.55 % moisture, because the ramp from −22 °C at 0.25 K/min takes 3.1 h of them. Six hours at 35 °C reach 1.95 % and stopper at 25.8 h, and ending on the assay waits for a result 45 min old and stoppers at 28.8 h with 1.38 %. A ramp of 1 K/min to 40 °C dries fastest and collapses every group with no ice left, the center 7.6 K over its glass transition, because the shelf outruns the moisture that sets the limit. These figures carry the weaker evidence of borrowed kinetics and a teaching X_0.

Table 5.6 Policies on the Challenge Batch at Six Paired Seeds. Cycle and Primary Drying in Hours, Worst Peak Over the Limit Per Group Across Seeds, Thermal Duty and Electricity Estimate as Seed Means

Policy (primary shelf, endpoint, secondary)	Pass	Cycle (h)	Primary (h)	Outer (K)	Inner (K)	Center (K)	Thermal (kWh)	Electric (kWh)
shipped: −22 °C, 19 h clock, 1 K/min to 40 °C, 3 h	0/6	22.01	19.00	+7.85	+8.37	+9.18	25.2	84.2
endpoint-aware, 1 K, learned $\hat{r}$, Pirani, est. moisture (suggested)	6/6	24.74–24.77	21.05–21.08	−0.39	−1.02	−0.96	26.5	91.6
the same without the learned $\hat{r}$ (ablation)	6/6	23.70–23.73	20.12–20.14	+0.08	−0.55	−0.18	26.3	89.0
the same with the estimator-and-gauges endpoint	6/6	25.59–25.64	22.05–22.09	−0.39	−0.68	−0.22	27.1	94.0
tuned recipe, strict: −23.5 °C, Pirani, 35 °C at 0.5 K/min	6/6	26.12–26.13	21.36	−0.06	−0.57	−0.86	26.3	94.5
tuned recipe, score only: −23 °C, same	6/6	25.68	20.93	+0.21	−0.31	−0.62	26.2	93.4
probe-limited, one probe each, 2 K, Pirani	0/6	31.60–31.62	25.08–25.11	+0.62	−0.24	−0.75	30.7	110.6
ideal-information bound, 1.75 K (reads the truth)	6/6	24.47	20.90	−0.62	−0.69	−0.22	26.2	90.7

✦ DID YOU KNOW? **Six Hours Are Not Enough at 25 Degrees**

From the simulator: secondary drying at a cool shelf is slow. Held at 25 °C, the center ends at 4.55, 2.83 and 1.75 % moisture after 4, 6 and 8 h (Table 5.5), so only the longest hold meets the 2 % limit at that shelf temperature.

5.6.5 Three Policies on the Challenge Batch

The challenge batch resists the vapor 15 % more than the calibration, and the nitrogen bleed sticks at 45 % for an hour from 5 h. The target is stoppering within 30 h with every group passing and the pressure never lost for more than 10 min. Table 5.6 compares the policies at six paired seeds, each seeing the same instruments with the same delays. The fixed recipe was re-tuned on this very batch over a logged grid of 96 runs (primary shelf, secondary target and ramp), and the strict choice is the fastest that keeps every group under its limit at every instant, −23.5 °C then 35 °C at 0.5 K/min.

The shipped recipe fails at every seed in three ways at once. Its clock ramps with 4.1 % of the center's ice left, its 1 K/min ramp collapses every group on its glass transition, and 3 h at 40 °C leave the center at 2.48 %. The endpoint-aware settings stopper at 24.74 to 24.77 h with every group at least 0.39 K under its limit at every instant, and the strict tuned recipe at 26.12 h, 1.38 h later. The gain is mostly not in primary drying. The endpoint-aware policy ends primary drying at 21.05 h against 21.36 h, 0.31 h sooner, and its secondary drying takes 3.69 h against 4.76 h, because it can ramp at 1 K/min while holding the shelf under the estimated glass transition. So 1.07 h of the 1.38 h rests on the weaker half of the model, as shown in Figure 5.2b. The ideal-information bound needs a 1.75 K margin to keep every group under its limit through the bleed fault and the shelf loop's lag (at 1 K it reaches 22.96 h but goes 0.48 K over), and it stoppers at 24.47 h, so the estimator comes within 0.28 h of perfect information. Probe-limited feedback with one probe on the edge fails at every seed, 0.62 K over on the outer edge, the pressure lost for 18 min and 31.6 h of cycle. Figure 5.3 draws the cycle and the worst peak of each policy.

The learned resistance is what keeps the margin. Without it the policy is faster, 23.70 h, because the estimator then believes the cake resists less and predicts a colder front, and it touches the limit by 0.08 K (0.2 K min, inside the score). The ablation is the cheaper policy on this batch, and it fails on the next one. Thermal duty barely separates the passing policies, 26.2 to 27.1 kWh, of which the condenser's refrigeration is 18.7 kWh in the endpoint-aware run, and the electricity estimate follows the cycle time because the pump runs throughout.

5.6.6 Sensitivity to Resistance and Heat Transfer

The batches of Table 5.7 change the product resistance or the center contact, and the estimator knows neither. Over 85 to 145 % resistance the endpoint-aware settings pass every case in 22.19 to 27.41 h, the closest group 0.29 K under. The recipe tuned for 115 % keeps its time but goes 0.29 K

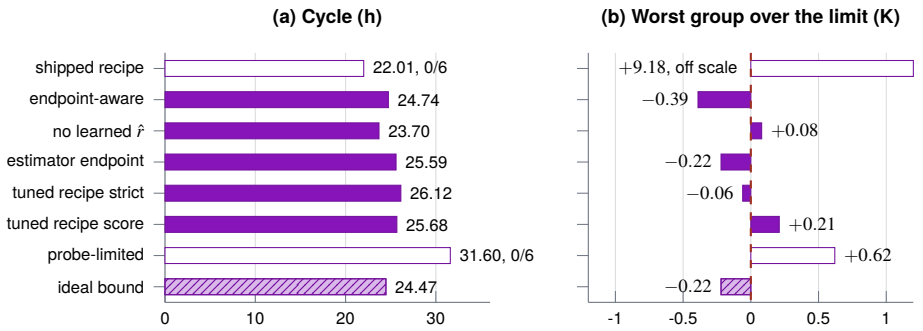


Figure 5.3 The policies of Table 5.6 on the challenge batch. (a) Cycle time, the lower end of the seed range where the table gives a range, with dark bars for policies that pass at all six seeds, white bars for those that pass at none and a light bar for the ideal-information bound. (b) The worst of the three groups' peaks over the limit, dashed line at the limit. Notice that the two fastest bars, the shipped recipe and the policy without the learned resistance, both cross the limit, and that the endpoint-aware policy ends within a fraction of an hour of the bound.

Table 5.7 Cycle (h) and Worst Peak Over the Limit (K) on Perturbed Batches, Default Seed. Bold: Fails

Batch	Tuned recipe	Endpoint-aware	Ablation	Bound
r 85 %	24.79, −0.65	22.19, −0.68	23.05, −0.99	**21.30**[a]
r 100 %	25.47, −0.44	23.44, −0.54	23.38, −0.45	22.88, −0.21
r 115 %	26.13, −0.06	24.74, −0.43	23.71, +0.03	24.47, −0.23
r 130 %	26.76, +0.29	26.07, −0.35	**24.11,** +0.47	26.04, −0.25
r 145 %	**27.39,** +0.61	27.41, −0.29	**24.46,** +1.22	27.61, −0.27
contact 85 %	**28.14**[b]	**28.08**[b]	**25.02,** +0.75[b]	25.69, −0.58
contact 70 %	**30.95**[b]	**32.58,** +0.39[b]	**26.95,** +1.76	27.02, −0.67

[a]pressure lost. [b]center over 2 % moisture. Contact rows at r 115 %.

over at 130 % (3.8 K min, a pass that depends on the score) and collapses its outer edge at 145 % (0.61 K, 18.5 K min), and the ablation collapses the outer edge at 130 % (13.6 K min). A contact loss defeats every policy that reads only the instruments. At 85 % contact the center ends at 2.00 to 2.04 % moisture under the endpoint-aware settings, the recipe and the ablation, just over the limit, because the moisture estimate does not know the contact either, and the assay samples the driest, front-row vials. Only the bound passes there. At 85 % resistance the bound itself fails, because driving the batch hard loses the pressure.

5.6.7 When the Gauge Law Is Wrong

The learned resistance is exact in this plant because the plant's Pirani obeys the linear law the estimator inverts and its duct has the declared conductance. Table 5.8 breaks each in turn. A Pirani that reads water vapor 1.7 times high instead of 1.6, a 6 % error, makes the estimator see more vapor than the batch makes and learn a cake that resists half as much ($\hat{r} = 0.52$). The endpoint-aware shelf then runs hot and every group collapses, 2.12 K over for 404 K min. A duct 20 % narrower than declared does the same, $\hat{r} = 0.50$, every group collapsed and the pressure lost for 90 min. Errors the other way are safe and slow, 4.1 to 4.6 h longer at factors of 1.4 and 1.5. A +0.3 Pa zero offset passes by 0.1 K min. The fixed recipe uses the Pirani only for its endpoint and passes every gauge case, and it fails only the narrow duct, through the plant's own pressure. The learning that buys robustness to resistance is therefore a single point of failure on the gauge law, and it is the main limitation of the method as implemented.

🕮 **Pause.** Try Exercise 5.3 before reading on.

Table 5.8 Plant and Estimator Mismatch on the Challenge Batch, Default Seed. Learned $\hat{r}$, Cycle (h) and Worst Peak (K)

Plant departs from the estimator	$\hat{r}$	Endpoint-aware	Verdict	Recipe
none (the app)	1.14	24.74, −0.43	pass	26.13, pass
Pirani factor 1.4	2.00	28.86, −2.02	pass	26.40, pass
Pirani factor 1.5	2.00	29.32, −1.90	pass	26.47, pass
Pirani factor 1.7	0.52	20.73, +2.12	all collapsed	26.06, pass
Pirani factor 1.8	0.50	21.05, +1.76	all collapsed	26.06, pass
zero offset −0.3 Pa	1.55	27.15, −1.43	pass	26.24, pass
zero offset +0.3 Pa	0.85	22.86, +0.56	pass, 9.9 K min	26.08, pass
duct 2.0 m^3/s	0.50	22.77, +1.55	all collapsed	26.79, fails
duct 3.0 m^3/s	1.86	28.24, −2.02	pass	26.03, pass

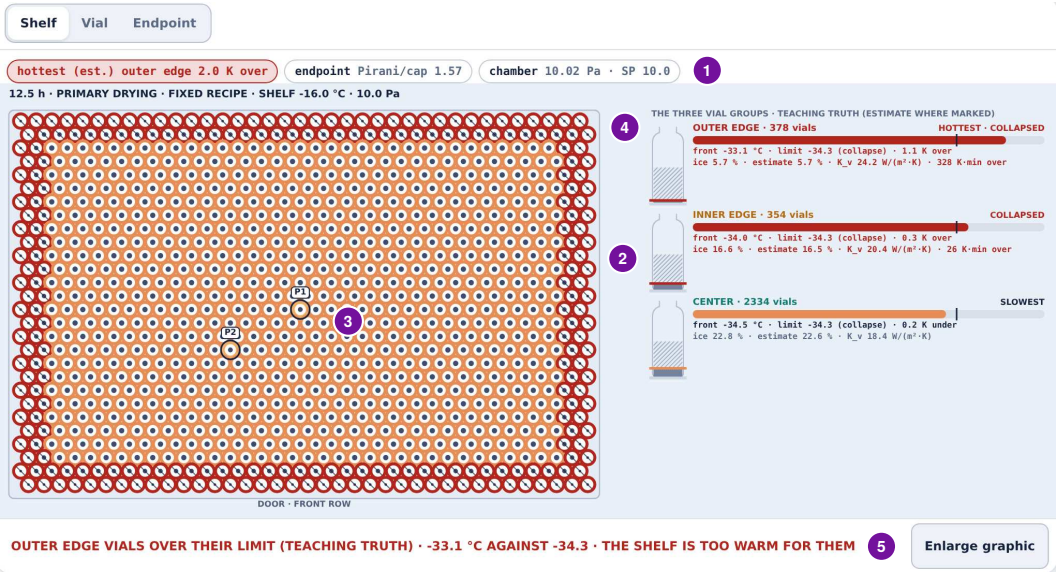


Figure 5.4 Excess shelf heat, case 2 at $t = 12.50$ h on the Shelf view, a fixed recipe at −16 °C and 10.0 Pa, cropped to the plant view. (1) The badges read the estimator's hot outer-edge vial 2.0 K over, a Pirani-to-capacitance ratio of 1.57 and the chamber at 10.02 Pa. (2) The shelf map rings every outer- and inner-edge vial red, (3) with the two probe vials in the center. (4) The group cards give the outer edge's front at −33.1 °C, 1.1 K over the limit with 5.7 % of its ice and 328 K min (collapsed and hottest), the inner edge at −34.0 °C, 0.3 K over with 16.6 % of its ice and 26 K min (collapsed), and the center at −34.5 °C, 0.2 K under with 22.8 % of its ice (slowest), with the estimator's ice within 0.2 points of each. (5) The status line names the outer edge as over its limit.

5.6.8 How Much the Score Decides

The 10 K min exposure is a convention, so its weight in the verdicts was measured. Of 48 distinct case and variant runs, 7 change a group's verdict if any excursion counts, 4 under a 1 K min score and 4 under 20 K min. In the 94 benchmark policy runs, 15 pass while over the limit at some instant, by at most 0.56 K and 9.9 K min. The endpoint-aware settings and the strict recipe never touch the limit, so the headline comparison does not depend on the threshold, while the recipe's pass at 130 %, the ablation's at 115 % and the offset case's pass do.

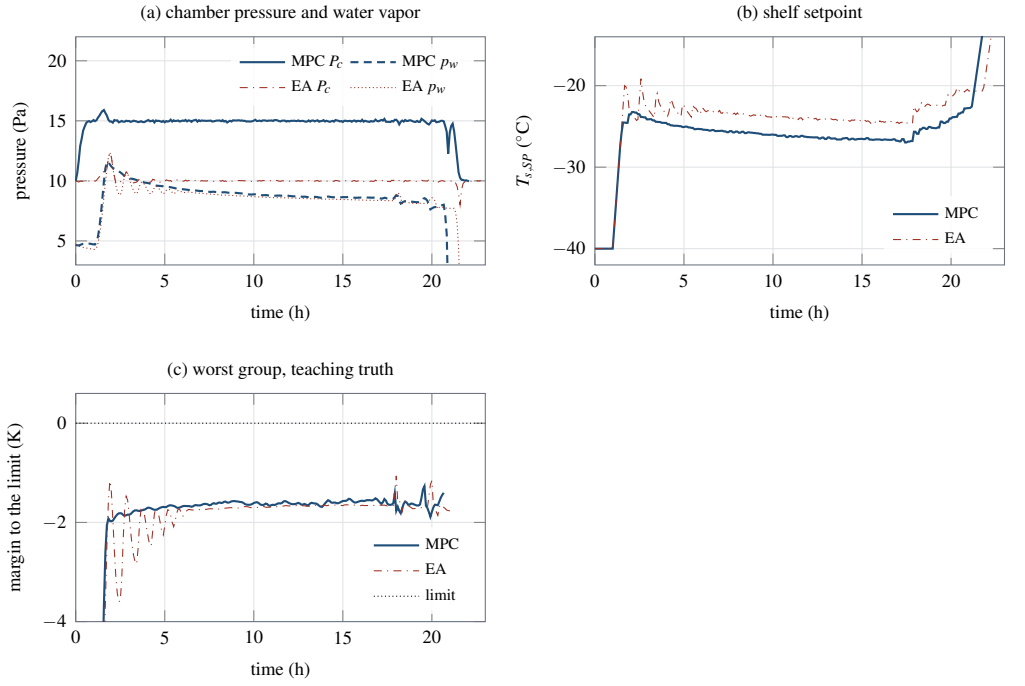


Figure 5.5 Case 9 under the predictive controller (MPC) and the shipped endpoint-aware policy (EA), default seed, logged every 5 min to an hour after primary drying. (a) Capacitance-gauge pressure (MPC solid, EA dash-dotted) and the chamber's water vapor (teaching truth, MPC dashed, EA dotted). (b) Shelf setpoint. (c) The worst group's margin to its limit (teaching truth). In (b) and (c) MPC is solid and EA dash-dotted.

5.6.9 Planning the Shelf and the Pressure Together

Case 9 loads the four shelves of case 3 (4088 vials, 11.87 kg of ice) with the shelf allowed up to 0 °C, a 1 K margin, the Pirani endpoint and the recipe's 10 Pa. It is the one shipped load on which the endpoint-aware policy loses the pressure at its recipe setpoint. Table 5.9 compares the policies on it, on case 1's batch with the same ceiling and endpoint, and on the challenge with its suggested settings, each run truth-scored to stoppering at the default seed with the same instruments. Its third group of rows answers the controller. The endpoint-aware policy retuned once by the controller's own rule over every knob it has (pressure 6 to 30 Pa, ramp 0.5 or 1 K/min, learning on or off, ceiling −10 or 0 °C) is the third row, and the strongest classical forms give the endpoint-aware policy the controller's pressure, either the top of its box or a high select on the measured vapor plus 2 Pa inside the box.

Under the controller, case 9's primary drying ends at 21.16 h against 21.81 h, the pressure is never lost against 36.7 min, the closest group stays 1.26 K under its limit against 0.91 K, and the shelf setpoint travels 31 K against 482 K, as shown in Figure 5.5. The plan raises the pressure setpoint to 15 Pa inside the vacuum hold (reached at 0.53 h) and holds a mean of 14.95 Pa through primary drying, where K_v is higher, while the vapor peaks at 11.62 Pa below it. Under the endpoint-aware policy the vapor passes 10 Pa at 1.68 h and first takes the pressure at 1.73 h, peaking at 12.36 Pa. The shelf trace of that policy saws because it recomputes the closed form every 10 s on noisy gauges, while the plan's moves are priced. On case 9 the product ceiling is active at 124 of 126 decisions with no positive slack, and the vapor row never binds (its closest predicted room is 1.16 Pa against the 1 Pa limit).

The gain is the pressure, not the horizon. Given the same 15 Pa, the endpoint-aware policy ends at 21.14 h, 19.08 h and 20.48 h on the three cases, a tie with the controller (21.16, 19.09 and 20.42 h).

Table 5.9 Predictive Controller Against the Rule-Based Policies, Default Seed, Truth-Scored to Stoppering. Closest Is the Least Margin of Any Group to Its Limit (Center in Parentheses), Negative Over It

	Case 9, four shelves				Case 1's batch		Challenge, suggested settings			
Policy	Primary (h)	Closest (K)	Lost (min)	Travel (K)	Primary (h)	Closest (K)	Primary (h)	Stoppered (h)	Closest (K)	Lost (min)
fixed recipe[a]	22.50	1.37 (2.48)	0	16	25.37	3.69	19.00	22.01	−9.17[b]	5.2
probe-limited, one each, 2 K	26.02	−1.43[c] (−0.41)	78.5	810	23.66	−0.50	—	—	—	—
endpoint-aware, 10 Pa (shipped)	21.81	0.91 (1.61)	36.7	482	19.63	0.90	21.05	24.74	0.43	0.5
predictive controller	21.16	1.26 (1.40)	0	31	19.09	1.11	20.42	24.13	0.85	0.2
endpoint-aware retuned, 30 Pa, 1 K/min	19.97	0.47 (0.93)	0	808	17.88	0.56	19.15	22.93	0.28	0
same rule, grid stopped at 25 Pa	20.24	0.52 (1.09)	0	791	18.15	0.62	19.44	23.20	0.33	0
endpoint-aware at the box top, 15 Pa	21.14	1.01 (1.58)	0	567	19.08	1.32	20.48	24.21	0.91	0.2
endpoint-aware, vapor high select	21.58	0.79 (1.55)	0	562	19.61	0.90	21.03	24.73	0.42	0.3
predictive controller, box 20 ± 5 Pa	20.37	1.45 (1.60)	0	28	—	—	—	—	—	—

[a] Case 9 −24 °C, case 1 −28 °C with the Pirani endpoint, challenge as shipped. [b] Three groups collapsed. [c] One group collapsed.
The controller solves 127, 115 and 123 times with no fallback.

Table 5.10 Worst Cases Under Every Structure. Groups Collapsed and K min Summed, Closest Approach to the Limit (K, Negative Over It), Pressure Lost (min). Load 3 Is Case 4's Batch, Load 4 Case 9's

Load, condition	Recipe	Probe, 2 K	Endpoint-aware	Same at 15 Pa	Retuned, 30 Pa	Controller, first build	Controller
3, none	0/0, 1.09, 0	0/4, −0.50, 24	0/0, 0.90, 0	0/0, 1.31, 0	0/0, 0.56, 0	0/0, 1.11, 0	0/0, 1.11, 0
3, resistance 160 %	1/238, −0.69, 0	1/11, −0.95, 0	0/0, 0.42, 0	0/0, 0.27, 0	0/2, −0.39, 0	0/0, 0.78, 0	0/0, 0.78, 0
3, condenser 30 %[a]	3/81590, −10.18, 3048	3/342, −2.57, 4700	0/0, 0.87, 2565	0/0, 0.81, 3166	0/0, 0.18, 0	0/0, 0.46, 66	0/0, 0.46, 66
3, duct 20 % narrower	0/0, 0.66, 0	1/14, −1.09, 64	3/91, −1.56, 82	3/580, −1.59, 0	3/333, −0.92, 0	3/641, −1.87, 0	0/0, 0.49, 0
3, T_c 1.75 K lower	1/194, −0.66, 0	3/237, −2.25, 24	1/22, −0.85, 0	1/63, −0.44, 0	2/172, −1.19, 0	1/60, −0.64, 0	1/57, −0.64, 0
4, none	0/0, 1.37, 0	1/28, −1.43, 78	0/0, 0.91, 37	0/0, 0.97, 0	0/0, 0.47, 0	0/0, 1.26, 0	0/0, 1.26, 0
4, condenser trip at 3 h	3/17528, −5.49, 1380	1/28, −1.43, 1337	0/0, 1.05, 849	0/0, 0.97, 0	0/0, 0.47, 0	0/0, 1.01, 0	0/0, 1.01, 0
4, resistance 60 %	0/0, 2.83, 23	1/15, −0.99, 728	0/0, 1.81, 168	0/0, 1.74, 0	0/0, 1.28, 0	0/0, 1.78, 0	0/0, 2.78, 0
4, resistance 160 %	1/21, −0.17, 0	2/40, −1.78, 30	0/0, 0.07, 16	0/0, 0.02, 0	0/3, −0.38, 0	0/0, 0.81, 0	0/0, 0.81, 0
4, contact 110 %	0/0, 1.26, 18	1/38, −1.55, 90	0/0, 0.41, 60	0/0, 0.43, 0	0/0, 0.36, 0[b]	0/0, 0.40, 0	0/0, 0.91, 0
4, condenser 30 %[a]	3/101438, −8.72, 4288	3/387, −3.58, 4706	0/0, 0.43, 3109	0/0, 0.19, 3277	0/1, −0.16, 0	0/0.3, −0.05, 97	0/0.3, −0.05, 97
4, duct 20 % narrower	0/0, 0.78, 311	3/52, −1.90, 152	1/16, −0.82, 371	3/429, −1.23, 0	3/192, −0.67, 0	3/588, −2.31, 0	0/0, 0.62, 0
4, T_c 1.75 K lower	1/91, −0.38, 0	3/298, −3.18, 78	2/79, −0.84, 37	2/139, −0.78, 0	3/267, −1.28, 0	2/129, −0.49, 0	2/127, −0.49, 0

[a]From the start, no structure finishes primary drying in 80 h. [b]Ice at the ramp, 0.02 %.

The third row ends case 9 at 19.97 h, 1.2 h before the controller, and the challenge at 19.15 h against 20.42 h of primary drying and 22.93 h against 24.13 h stoppered, with margins of 0.47 and 0.28 K against 1.26 and 0.85 K. The first grid of that rule stopped the pressure at 25 Pa and picked 20.24 h. Extended to the control's full range without changing the rule, it picks 30 Pa. With its box moved to 20 ± 5 Pa the controller ends at 20.37 h, within 0.13 h of the endpoint-aware policy at 25 Pa, so the pressure box sets the time. Over margins from 0 to 2 K on case 9 the controller ends 0.60 to 1.08 h before the endpoint-aware policy at 10 Pa, which loses the pressure for 15.5 to 73.3 min at every margin while the controller never does. When the condenser's refrigeration falls to 50 % at 3 h of case 9, the endpoint-aware policy loses the pressure for 849 min and ends primary drying at 34.28 h, while the controller loses none and ends at 31.94 h. One case is lost on margin. With the challenge's suggested settings and the estimator-and-gauges endpoint, the controller ends primary drying at 21.35 h against 22.05 h but brings the center to 0.13 K under its limit against 0.22 K, because after the hot copies enter their tails it keeps the colder copies at the limit.

The worst cases were run under every structure on case 4's batch (shelf target −22 °C for the recipe) and on case 9's (−24 °C), 18 conditions each, to stoppering or 80 h, as shown in Table 5.10. In the 26 runs of conditions the estimator knows or measures (none, the bleed stuck at 1.5 or 3 h, the condenser trip, the shelf fluid held, contact 70, 85 and 110 %, resistance 60, 145 and 160 %, probe bias ±3 K, on both loads), the controller collapses nothing, loses the pressure for at most 0.3 min and keeps every group at least 0.78 K under. In the same runs the endpoint-aware policy collapses nothing (closest 0.07 K) but loses the pressure for more than 10 min in 14 (12.8 to 849 min), the third row goes 0.19 to 0.39 K over at 145 and 160 % resistance, probe-limited feedback collapses a group in 16 and the recipe in 5. The condenser's ice never exceeds 11.9 kg of its 15 kg, and every run that finishes ends at or below 1.41 % moisture.

The controller's first build was less safe than the shipped policy in one condition. With the duct 20 % narrower than declared, the estimator turns the duct's shortfall into a learned resistance that falls to its 0.50 clamp, every copy reads cold, and the first build collapsed all three groups on both loads (641 and 588 K min). The endpoint-aware policy collapses three and one group (91 and 16 K min) and is held back on four shelves only by its bleed rule while it loses the pressure for 371 min, and given 15 Pa it collapses all three as well (580 and 429 K min). The revised plan judges the vials with $\max(\hat{r}, 1)$, the platform's declared value chosen before any run, so the learning can only make it more careful. After the change nothing collapses on either load (closest 0.49 and 0.62 K under, the pressure held, primary drying 22.95 h on four shelves), every comparison case moved by at most 0.01 h (case 9 from 21.153 to 21.156 h), and the tuning rule re-run keeps the same weights. The price falls where $\hat{r} < 1$ is genuine. At 60 % resistance primary drying lengthens from 17.81 to 19.67 h on four shelves and from 15.78 to 17.58 h on three, and with the center contact at 110 % from 19.59 to 20.39 h. Given to the endpoint-aware policy, the same floor also saves the narrow duct (no collapse,

24.62 h, the pressure lost for 125 min).

Two worst cases remain against the controller. A collapse temperature 1.75 K lower than the controls are told collapses groups under every structure, and the controller collapses as many as the endpoint-aware policy with more exposure (57 against 22 K min on three shelves, 127 against 79 K min on four). The cause is the pressure, because the endpoint-aware policy at 15 Pa gives 63 and 139 K min, and only the learner's margin can cover a limit no control is told. With the condenser at 30 % from the start no structure finishes, and on four shelves the controller goes 0.05 K over for 11 min (0.3 K min, not collapsed) where the endpoint-aware policy stays 0.43 K under. Its model holds the coil temperature constant over the horizon, and at 1.8 to 2.1 h the vapor stands 3.4 to 6.5 Pa above the pressure the plan set.

5.7 Technology in Practice

What Measures It

Thermocouples are preferred for the product because they measure at a point, best at the center of the vial bottom, while resistance temperature detectors read fixed points such as the shelf fluid at its inlet manifold [17]. Putting a probe into an open vial is a manual step, so production probes often sit only in the front row, a location the edge effect makes unrepresentative, and the probed vials may dry faster than the rest of the batch [17]. The simulator gives its probed vials 80 % of a normal vial's resistance, and cases 6 and 7 show what such probes do to a cycle.

> **TECHNOLOGY Sensor: A Pirani Gauge Beside a Capacitance Manometer**
>
> A capacitance manometer has a sealed, evacuated reference side and a metal diaphragm that flexes with the process pressure and changes a capacitance, so it reads the true pressure whatever the gas. A Pirani gauge holds a heated filament at constant temperature and reports the current that takes, which depends on the gas: the free molecular conductivity of water vapor is about 60 % higher than that of nitrogen. Calibrated with nitrogen, the Pirani reads high while ice sublimes and falls to the manometer's reading as the ice runs out. The manometer is accurate to about 0.25 % of reading, a Pirani gauge to 5 to 25 %. Pirani filaments can fail under repeated steam sterilization, and a vial fallen to the floor can fool the comparison [17].

What Moves It

Two final elements act on the batch. The fluid circulated through the shelves heats and cools the product, and a gas bleed, the dryer's vacuum control, sets the chamber pressure to improve the heat transfer to the product [13]. In a dryer controlled on the Pirani gauge, the nitrogen flow rises as the water vapor falls, which raises the true pressure, the heat transfer and the product temperature near the end of primary drying [17]. PIC-102 trims the bleed from the capacitance gauge, and because a bleed can only add gas, the valve shuts and the pressure is lost when the vapor alone exceeds the setpoint, as in case 3.

> **TECHNOLOGY Final Element: Shelves Fed by a Heat Transfer Fluid**
>
> The shelves of a freeze-dryer are heat exchangers with a serpentine liquid path, and a heat transfer fluid such as silicone oil circulates through them for heating and cooling the product [13]. The reading called shelf temperature is the fluid's inlet temperature, taken just upstream of the manifold that feeds every shelf, and the difference between inlet and outlet is proportional to the thermal load on the shelves [17]. One laboratory dryer's fluid system ran between −40 °C and 50 °C, cooling at 0.8 °C/min and heating at 1 °C/min at most [1]. Shelf fluid leaking into the chamber is cause to reject the batch [13]. TIC-101 stands for this loop with a thermal-unit duty between −2.5 and 3.0 kW.

Where the Controller Runs

One laboratory dryer retrofitted for model-based control ran its condenser, shelf and pressure loops as on-off controllers in programmable logic controllers. A remote supervisory computer drove the

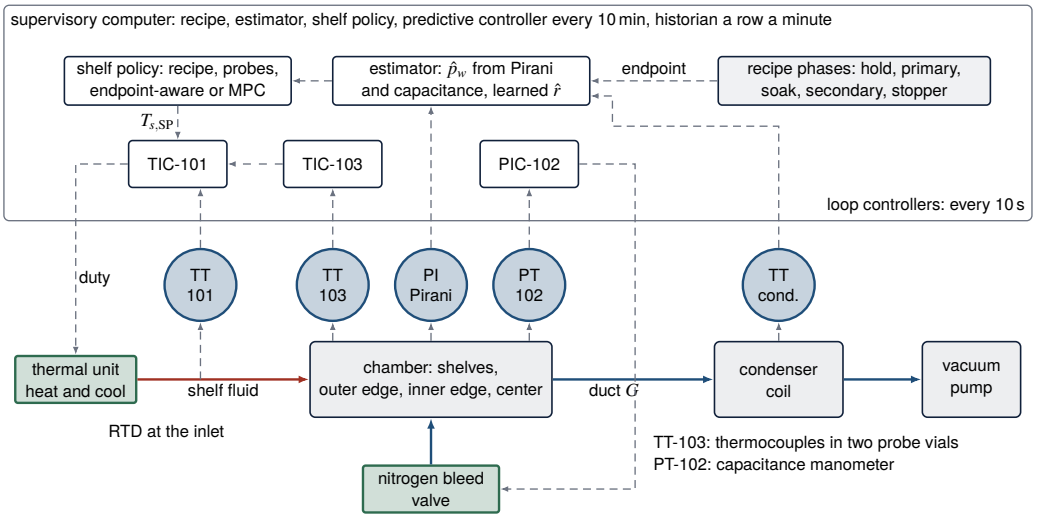


Figure 5.6 The chapter's loops on plant hardware. TIC-101 reads the RTD TT-101 at the shelf fluid inlet and sets the thermal unit's duty. PIC-102 reads the capacitance manometer PT-102 and moves the nitrogen bleed valve. TIC-103, in the probe-limited policy only (dashed), lowers the shelf target from the two probe thermocouples. The estimator reads the vapor from the Pirani and capacitance gauges and the condenser thermometer, and the shelf policy or the predictive controller sets the shelf target. Notice that no loop reads the product temperature of the unprobed vials.

dryer through its sequential steps, from freezing through primary and secondary drying to venting and stoppering, and the model-based strategy for primary drying sat on top of the low-level loops [1]. The batch control committee of ISA describes a functional model that relates recipe management, scheduling, sequential control, regulatory control and safety interlock systems [22]. Read in those terms, the vacuum hold, primary drying, the soak and secondary drying are the phases of one recipe, the endpoint rules are its transitions, and TIC-101, PIC-102 and TIC-103 are the regulatory control. Such loops run with cycle times from milliseconds to minutes [23], and the simulator's loops execute every 10 s, the predictive controller plans every 10 min, and the historian logs a row a minute, the rate best practice asks for to catch transient events [17]. Figure 5.6 draws the loops on plant hardware.

> **IN PRACTICE** **Commissioning the Pressure Pair**
>
> Best practice controls the chamber pressure on the capacitance manometer, with a temperature-controlled sensing head, and watches a Pirani gauge beside it. A capacitance manometer is calibrated against another one as a transfer standard, never against a thermal or mechanical gauge, and one on a steam-sterilized dryer is recalibrated every 3 months. Calibrating the Pirani matters less, because only its changes are read. Before the shelf is raised for secondary drying, the Pirani reading should nearly reach the manometer's: a difference of 5 to 10 millitorr works while the primary-drying pressure is above about 40 millitorr [17]. The simulator's ratio of 1.07 for 15 min plays that part.

What Is Modernizing It

Tunable diode laser absorption spectroscopy measures the concentration and the flow of water vapor in the duct between chamber and condenser with two lasers and two detectors, a non-invasive, in-line reading of the batch sublimation rate from which the heat and mass transfer coefficients are calculated [24]. It is the measurement the chapter's estimator reconstructs from two gauges and a declared duct. Wireless product sensors read probed vials without lead wires [17]. Model-based supervision that propagates the uncertainty of its heat transfer and resistance fits has run primary

drying at an accepted risk of failure [1], the strategy on which this simulator's primary drying is calibrated.

5.8 Limitations

Primary drying is calibrated on one laboratory study of one formulation in one vial, and its agreement with that study is consistency, not validation. Each group is one vial with no scatter, the front is flat, freezing is a checkpoint, and the chamber, duct, condenser, pump and thermal unit are teaching values for a pilot dryer, with no choked flow. Secondary drying borrows its kinetics and glass-transition law from another formulation, starts from a teaching bound water, and carries most of the measured advantage of the endpoint-aware policy. The collapse score is a convention that lets brief excursions pass, and a collapsed group carries no potency loss. The estimator inverts exactly the Pirani law and duct the plant obeys, so its learned resistance is optimistic here, and a 6 % error in the gauge factor or a 20 % narrower duct collapses every group. One measured flow cannot separate resistance from heat transfer, so a contact loss is read as resistance, and the moisture estimate misses it. The predictive controller's model inherits those blind spots and adds its own. It drops the vial's sensible heat (carried only as a decaying correction), desorption in primary drying, the thermal unit's saturation, the coil warming over the horizon and the condenser's narrowing near its ice capacity, its pressure lag omits the PI's feedthrough, and the floor on the learned resistance costs up to 1.86 h where a batch truly resists less. Energy is thermal duty, and the electricity figure rests on declared efficiencies. The comparison is on one batch design with six seeds whose noise barely moves the result (cycle ranges under 0.05 h), so seed spread is not an uncertainty estimate for a real dryer.

> **OPEN CHALLENGE** **The Vials Nobody Measures**
>
> The product temperature decides the cake, yet it cannot be controlled directly [24]. A thermocouple measures one point in one vial, inserting it by hand compromises sterility assurance, and production probes therefore often sit in the front row, where the edge effect makes them unrepresentative and the probed vials may dry faster than the batch. Wireless sensors avoid the lead wires, but in 2017 there was little published experience with them and best practices for them were called premature [17]. Progress would be a reading of the unprobed center vials that works with automatic loading.

5.9 Conclusion

A shelf of identical vials dries as a population, and this simulator keeps each group's ice, front and moisture beside what two thermocouples, two gauges, an assay and an estimator report. At 10 Pa the outer edge takes 32 % more heat than the center, dries 3.2 h sooner under a fixed shelf and comes 1.3 K closer to its limit, so the hottest group sets the shelf and the slowest sets the endpoint. A fourth shelf makes more vapor than the declared duct passes, and no setting of 115 meets an 18 h target. Probes in the center protect themselves while every group collapses, and front-row probes ramp with 18.6 % of the center's ice left. On the challenge batch an endpoint-aware policy stoppers 1.38 h before a recipe tuned for that batch and within 0.28 h of a bound that reads the truth, and it keeps its margin from 85 to 145 % resistance, but 1.07 h of its gain lies in secondary drying and its learned resistance fails on a 6 % gauge error. A predictive controller on the estimator's model holds the pressure on four shelves where that policy loses it for 36.7 min, with 31 K of shelf travel against 482 K, while the same policy retuned to 30 Pa ends primary drying 1.2 h sooner at a smaller margin. The model is lumped, calibrated on one study and optimistic about its own instruments. Further work would add vial scatter within groups, a nonlinear Pirani response with drift, a calibrated secondary-drying model for the same formulation, and an estimator that tests its gauge law before it learns from it. The simulator shows that a freeze-drying cycle is only as good as its knowledge of the vials it does not measure.

KEY POINTS

- A shelf of identical vials dries as a population: the edge vials take more heat and dry sooner, and the center vials dry last.
- At 10 Pa the outer edge takes 32 % more heat than the center, so the hottest group sets the shelf and the slowest the endpoint.
- Front-row probes ramp with 18.6 % of the center's ice left.
- An endpoint-aware policy stoppers 1.38 h before a tuned recipe, but 1.07 h of the gain lies in secondary drying.
- A predictive controller's measured gain is the chamber pressure it may set, not cycle time.

Where else this applies. The glass-transition law that limits the cake in secondary drying also sets the sticky point of milk powder in Volume 5, Chapter 10, where moisture and a glass transition are likewise inferred from slow measurements.

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5.10 Exercises

5.1 ⌕ Concept check · 2 min

Case 4 dries the pilot batch under a fixed shelf at −22 °C, 10 Pa and the Pirani endpoint. Which statement describes the three vial groups?

(a) The outer edge comes closest to the collapse limit and dries first, while the center dries last, so the edge sets the shelf and the center sets the endpoint

(b) The center comes closest to the limit because it holds ice longest, while the outer edge dries first and so sets the endpoint

(c) The three groups dry within minutes of each other, so one representative vial can set both the shelf and the endpoint

(d) The outer edge dries last, because the radiation it receives from the walls warms its cake instead of its ice

5.2 ⌕ Concept check · 2 min

In case 3 four shelves at −18 °C lose the chamber pressure for 737 min although PIC-102 is in Auto at 10 Pa. Why can the loop not hold its setpoint?

(a) Its integral time of 120 s is too long for the vapor surge, and a faster tuning would hold the setpoint

(b) The bleed can only add nitrogen, so once the vapor alone exceeds the setpoint the valve shuts and the vapor path sets the pressure

(c) The condenser coil warms past its duty and stops condensing, so water vapor accumulates in the chamber

(d) The capacitance gauge reads only the nitrogen, so the loop sees 10 Pa while the chamber is above it

5.3 ⌕ Concept check · 2 min

The estimator infers the water vapor as $\hat{p}_w = (P_{Pir} - P_{cap})/0.6$, the linear Pirani law with a factor of 1.6. Suppose the plant's Pirani in fact reads water vapor with a factor of 1.7. What happens to the endpoint-aware policy on the challenge batch?

(a) The Pirani ratio falls below 1.07 sooner, so primary drying ends with ice left in the center
(b) The estimator sees less vapor than the batch makes, learns a more resistant cake and runs the shelf cold and slow
(c) The estimator sees about a sixth more vapor than the batch makes, learns a cake that resists about half as much, and the shelf runs hot enough to collapse every group
(d) Nothing changes, because the learned multiplier is clipped between 0.5 and 2 and the Pirani is used only for the endpoint

5.4 Theory and calculation · 5 min

The vial heat transfer coefficient is $K_v = \alpha + \beta P_c/(1+\gamma P_c)$ in W/(m^2 K) with P_c in pascals. The calibration fits are $\alpha = 3.46$, $\beta = 1.93$, $\gamma = 0.0292$ for a center vial and $\alpha = -1.14$, $\beta = 4.46$, $\gamma = 0.0757$ for an outer-edge vial.

(a) Compute both coefficients at 10 Pa and the edge's extra heat for the same shelf-to-bottom difference. *Checkpoint:* 18.40 and 24.24 W/(m^2 K), 32 %.

(b) The inner edge sits 35 % of the way from center to edge. Compute its coefficient at 10 Pa. *Checkpoint:* 20.44 W/(m^2 K).

(c) The predictive controller of case 9 raises the pressure to 15 Pa. Compute both coefficients there, the relative rise of each and the new edge-to-center ratio. *Checkpoint:* 23.59 and 30.19, rises of 28.2 % and 24.5 %, ratio 1.280.

5.5 Theory and calculation · 6 min

The vapor leaves the chamber through a duct of declared conductance $G = 2.5\,\mathrm{m^3/s}$ to a coil at T_{cd}, so the condenser takes $W_{cd} = \frac{M_w G}{R T_{gas}}\left(p_w - p_{ice}(T_{cd})\right)$ with $M_w = 18.015\,\mathrm{g/mol}$, $R = 8.314\,\mathrm{J/(mol\,K)}$ and $T_{gas} = 293.15\,\mathrm{K}$. The ice vapor pressure is the last line of Equation (5.1).

(a) Compute p_{ice} at a coil temperature of −73.2 °C. *Checkpoint:* 0.161 Pa.

(b) Compute the vapor the duct carries with 10 Pa of water vapor in the chamber, in kg/h. *Checkpoint:* 0.654 kg/h.

(c) Four loaded shelves hold 11.87 kg of ice and three hold 8.90 kg. How long would each take to sublime at that rate, and what does that say about an 18 h target for primary drying? *Checkpoint:* 18.1 h and 13.6 h.

5.6 Theory and calculation · 6 min

Secondary drying follows Equation (5.4) with $k_{d,0} = 277\,\mathrm{s^{-1}}$, $E_{a,d} = 37\,714\,\mathrm{J/mol}$ and the Gordon–Taylor constants $K = 0.2721$, $T_{g,w} = 135\,\mathrm{K}$, $T_{g,s} = 347\,\mathrm{K}$. The moisture is $w = X/(1+X)$ and the limit at stoppering is $w = 2\,\%$.

(a) Compute the cake's glass transition when the ice leaves, at $X_0 = 0.08\,\mathrm{kg/kg}$, and at the moisture limit. *Checkpoint:* 25.7 °C and 59.1 °C.

(b) Below which moisture may the cake meet a shelf at 40 °C without passing its glass transition? *Checkpoint:* $w = 4.9\,\%$.

(c) Compute the desorption time constant at 25 °C and at 40 °C, and the time a fully dry cake held at 40 °C needs to fall from X_0 to the limit. *Checkpoint:* 4.1 h and 2.0 h, then 2.7 h.

5.7 App challenge · 8 min

Load scenario 1, A conservative recipe. Keep Auto, the default seed and the shipped settings, and set the speed to 3600, which runs an hour of the batch in a second.

(a) Run until the batch is stoppered and the run pauses. From the exported CSV, read the hour at which each group's ice first reaches zero (columns `truth_ice_o_pct`, `truth_ice_i_pct` and

`truth_ice_c_pct` against `hours`). Read the tiles Cycle time, worst group and Hottest group · peak over its limit. *Checkpoint:* 21.2 h, 23.6 h and 25.1 h, stoppered at 50.0 h, outer edge −3.7 K.

(b) Press Reset, set End primary drying when to Pirani meets capacitance (Endpoint view) before pressing Run, and run to stoppering. Read the hour primary drying ended, the first row whose `phase` is not `primary`, and the cycle time. *Checkpoint:* 25.4 h, stoppered at 35.4 h.

How many hours of the recipe's primary drying dried nothing? Give hours to within 0.1 h.

5.8 App challenge · 8 min

Load scenario 7, A premature primary-drying endpoint: both product probes in front-row vials, the shelf at −22 °C and primary drying ended when both probes reach the shelf. Keep the default seed and set the speed to 3600.

(a) Run to stoppering. From the CSV read when the probe vials ran out of ice (`truth_ice_p1_pct`) and when primary drying ended (the first row whose `phase` is not `primary`). Read the tiles Slowest group and Hottest group. *Checkpoint:* Probes dry at 15.4 h, ramp at 16.0 h, center 18.6 % of its ice at the ramp, +7.2 K, 286 K min.

(b) Press Reset, set End primary drying when to Pirani meets capacitance before pressing Run, and run to stoppering. Read the same hour and the cycle time. *Checkpoint:* Ramp at 19.8 h, stoppered at 29.8 h, all groups pass.

Why did the probe rule end primary drying early, and what did that cost? Give hours to within 0.1 h, the ice share to within 0.2 points, the peak to within 0.1 K and the exposure to within 2 K min.

5.9 App challenge · 9 min

Load scenario 9, MPC: the product limit and the condenser together (four shelves, Shelf policy on MPC). Keep the default seed and set the speed to 3600. For each run, read the hour primary drying ended from the CSV (the first row whose `phase` is not `primary`) and the minutes on the tile Condenser · pressure held.

(a) Run the scenario as loaded to stoppering. *Checkpoint:* 21.16 h, 0 min lost.

(b) Press Reset, set Shelf policy, primary drying to Endpoint-aware (estimator) on the Recipe card before pressing Run, and run to stoppering. *Checkpoint:* 21.81 h, 37 min lost.

(c) Press Reset, keep the endpoint-aware policy, set Chamber pressure, primary drying to 15 Pa, and run to stoppering. *Checkpoint:* 21.11 h, 0 min lost.

What does the predictive controller add on this load? Give hours to within 0.03 h and minutes to within 1 min.

5.10 Application area · 4 min

A filling plant puts both product thermocouples in front-row vials, because those are the only vials an operator can reach without disturbing the loaded shelves under sterile handling, and it ends primary drying when both probes reach the shelf. What does the chapter predict, and what would you recommend?

5.11 Application area · 4 min

A manager reads that the endpoint-aware settings stopper the challenge batch 1.38 h sooner than the best tuned recipe and proposes changing a validated production cycle on that evidence. What does the chapter's evidence support, and what would you require first?

5.12 Review the agent · 5 min

An AI assistant runs the challenge with Reveal suggested tuning, then again with Estimator learns the batch's resistance from the chamber set to Off (Advanced). It reports: "With learning off the batch stoppers at 23.7 h instead of 24.7 h, every group passes and the challenge target is met. The learned

resistance only slows the cycle, so ship the settings with learning off.” Find the flaw and say how you would check it.