

Title

SuperFract™ Adaptive-Dosing Precipitation Control

Description

Background of the Invention

Plasma-protein fractionation today is governed by “grab-sample” practice: operators draw 10–20 mL from a 1 000–3 000 L precipitation tank every 15–30 minutes, clarify it by centrifuge or filter, and analyse protein concentration offline by UV-280 or Kjeldahl. The analytical turnaround is typically 10 – 30 minutes, during which the batch continues to agitate and cool. To avoid waiting, operators routinely overdose ethanol or polyethylene-glycol by 5 – 10 % v/v and prolong mixing to “guarantee” completion. This safety margin lowers IgG yield by 2 – 4 percentage points, increases solvent-recovery energy cost, and loads filters with excess precipitate, causing premature fouling and higher filter spend.

Offline sampling also introduces compliance and biosafety pain-points. Manual dip-samplers breach the closed GMP environment, demanding separate laminar hoods or isolators; each breach must be logged and disinfected, extending clean-room labour. Sample tubes create traceability gaps—mis-labels, delayed lab uploads, or transcription errors—that complicate deviation investigations and FDA audits. Because sampling is sparse, process deviations such as vortex entrainment, jacket hot-spots, or sensor drift remain undetected for an entire batch, forcing expensive re-work or discard. Industry therefore needs an in-situ, self-validating precipitation monitor that delivers second-by-second feedback, minimises over-dose, and records a continuous digital batch history without manual sampling.

1. Field of the Invention

Real-time, closed-loop control of plasma-protein precipitation steps (ethanol, PEG, ammonium-sulfate, caprylic-acid, pH-shift, temperature-shift, or hybrid) using fused at-line/inline analytics and adaptive reagent-dosing algorithms.

2. Background

Conventional fractionation relies on manual grab-samples every 15–30 min. Each sample is clarified and assayed offline, adding a 10–30 min delay. Operators therefore overdose precipitant by 5–10 % v/v, lowering IgG yield, increasing solvent-recovery cost and accelerating filter fouling. Dip-sampling also breaks aseptic containment, generates mis-label risk and leaves long gaps during which vortex entrainment or sensor drift remain undetected. A self-validating, in-situ monitoring and dosing system is needed.

3. Summary

Liquor is withdrawn through isolation valve **XV-301 (801-2)** and pump **P-201 (801-3)** into flow-cell **FC-301 (801-4)** that houses optical sensor **NTU-301 (801-5)** and ultrasonic sensor **US-302 (801-6)**. Optional clarifier splitter **XV-311 (802-2)** routes slip-stream through micro-filter **CF-401 (802-3)** and UV-detector **UV-401 (802-4)**. A fusion library (controller **FUS-900**) computes precipitation estimate $\hat{P}\%$ and modulates reagent pump **PD-202 (801-9)**. Filtration unit **F-501** with pressure taps **PT-501A/B (809-1, 809-2)** provides trans-membrane-pressure (TMP) slope; valve **XV-403 (809-4)** routes liquor forward or back. Fourteen embodiments cover sensor modalities, control algorithms and self-test schemes.

4. Brief Description of the Drawings

FIG. 801—Side-loop dual-sensor circuit. *FIG. 802*—Tri-sensor loop with UV clarifier. *FIG. 803*—Inline acoustic-resonance probe. *FIG. 804*—Disposable dielectric-spectroscopy cartridge. *FIG. 805*—Laser-diffraction particle analyser. *FIG. 806*—Model-predictive control architecture. *FIG. 807*—Rule-based adaptive recipe. *FIG. 808*—Machine-learning anomaly guard. *FIG. 809*—Cross-flow-filtration ΔP feedback. *FIG. 810*—Pulse-width-modulated dosing. *FIG. 811*—pH-shift / PEG cascade. *FIG. 812*—Temperature-ramped ethanol cut. *FIG. 813*—Cloud-supervised digital twin. *FIG. 814*—Self-testing probe cartridge.

5. Detailed Description

5.1 Embodiment E-1 – Side-Loop Dual-Sensor Control (FIG 801)

Hardware: XV-301 (801-2), P-201 (801-3), FC-301 (801-4), NTU-301 (801-5), US-302 (801-6), PRX-303 (801-7), return valve XV-302 (801-8). Pulse–pause–measure (30 s dose, 45 s mix, 15 s read), EWMA $\alpha = 0.2$, fusion weight NTU 0.5 / US 0.5. Calibration: gravimetric; proceed threshold $90 \pm 2 \%$.

5.2 Embodiment E-2 – Tri-Sensor with UV-Clarifier (FIG 802)

Adds splitter XV-311 (802-2), cartridge CF-401 (802-3), detector UV-401 (802-4), return valve XV-312 (802-5). Slip-stream 10 mL min^{-1} , 8 s every 90 s. Fusion weights NTU 0.35 / US 0.35 / UV 0.30.

5.3 Embodiment E-3 – Inline Acoustic-Resonance Probe (FIG 803)

Probe 803-1 welded in vessel; resonance circuit 803-2 feeds controller FUS-900 (803-3). Δf sampled 10 Hz; weight 0.35; bubble spike $> 15 \text{ Hz s}^{-1}$ disengages.

5.4 Embodiment E-4 – Dielectric-Spectroscopy Cartridge (FIG 804)

Single-use body 804-1; twin electrodes 804-2; impedance chip 804-4. Sweep 100 kHz–10 MHz, ϵ'' peak @ 1 MHz; fusion weight 0.30.

5.5 Embodiment E-5 – Laser-Diffraction Analysis (FIG 805)

Laser 805-1, scattering cell 805-2, photodiode array 805-3, processor 805-4. PSD→XGBoost model; fusion weight 0.25.

5.6 Embodiment E-6 – Model-Predictive Control (FIG 806)

Sensor vector 806-1 feeds state-space model 806-2; optimiser 806-3 sends actuator output 806-4 under constraints 806-5.

5.7 Embodiment E-7 – Rule-Based Recipe (FIG 807)

PLC ladder 807-1 reads LUT 807-2; setpoint trim 807-3; alarm block 807-4.

5.8 Embodiment E-8 – Anomaly Guard (FIG 808)

Feature extractor 808-1 → GBT classifier 808-2 → confidence 808-3 → failover FSM 808-4; passes good frames to FUS-900.

5.9 Embodiment E-9 – Filtration ΔP Feedback (FIG 809)

PT-501A (809-1) & PT-501B (809-2) feed TMP calc 809-3; valve XV-403 (809-4) routes permeate to next tank or recycle line 809-5.

5.10 Embodiment E-10 – PWM Dosing (FIG 810)

Duty-cycle controller 810-2 drives pump 810-1; flow feedback 810-3; anti-chatter logic 810-4.

5.11 Embodiment E-11 – pH-Shift / PEG Cascade (FIG 811)

PD-210 (811-1) & pH sensor PT-103 (811-2) complete Stage-1; PD-211 (811-3) metered via fusion-control output 811-4.

5.12 Embodiment E-12 – Temperature-Ramped Ethanol (FIG 812)

Jacket J-101 (812-1), controller 812-2, pump 812-3, ramp generator 812-4; $-5\text{ }^{\circ}\text{C}$ to $+10\text{ }^{\circ}\text{C}$ over 20 min.

5.13 Embodiment E-13 – Cloud-Supervised Twin (FIG 813)

Edge PLC 813-1 → MQTT broker 813-2 → cloud ML 813-3 → update agent 813-4 back to PLC.

5.14 Embodiment E-14 – Self-Testing Cartridge (FIG 814)

Auto-zero chamber 814-1, micro-valves 814-2, optical test path 814-3, acoustic test path 814-4, self-test circuit 814-5.

6. Common Hardware & Sanitation

All wetted metal 316L SS $\leq 0.5\text{ }\mu\text{m Ra}$; plastics USP <88> Class VI. Reusable flow-cells undergo SIP $\geq 20\text{ min @ }121\text{ }^{\circ}\text{C}$; single-use cartridges γ -sterilised 25 kGy. FC-301 pressure-rating 6 bar; cartridge 2 bar.

7. Critical Process Parameters (CPP)

CPP	Nominal	Permissibl	Alarm	Trip
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Temperature TT-102	-5 °C	-7...+2 °C	±3 °C	±5 °C
pH PT-103	5.2	5.0–5.4	±0.3	±0.5
EtOH conc. AIT-203	8 % v/v	±0.5 %	±1 %	±2 %
$\hat{P}\%$	≥ 90 %	88–92 %	< 88 %	< 85 %

8. Validation & Fallback

Process-qualification matrix: ≥ 5 lots × 3 temps × high/nominal/low reagent. Sensor disagreement > 2 σ 60 s ⇒ freeze dosing, run UV clarify; TMP slope > 200 kPa min⁻¹ first 5 min ⇒ recycle & dose +0.5 % EtOH.

2. Summary of Embodiments

Below are 14 mutually non-exclusive embodiments

#	Title	Core Idea	Distinguishing Features	Primary Figures
E-1	Side-Loop Dual-Sensor Control	Continuous slipstream (0.2–0.8 L min ⁻¹) through turbidity (NTU-301) and ultrasonic (US-302) sensors; fusion signal drives pulse–pause–measure dosing.	No sensors inside main tank; loop is CIP/SIP compatible.	FIG. 801-A-1 to 801-A-4

E-2	Tri-Sensor with UV-Clarifier	Adds clarified micro-filter branch (CF-401 → UV-401) every 60–120 s for UV-280 “truth” anchor; Kalman-filtered fusion (FUS-900).	Improves accuracy; handles optical fouling drift.	FIG. 802-B-1
E-3	Inline Acoustic Resonance Probe	38 kHz piezo in tank wall; measures resonance shift proportional to solids volume fraction.	Works in stainless CIP tanks; handles opaque liquids.	FIG. 803-C-1
E-4	Inline Dielectric Spectroscopy Cartridge	Disposable single-use smart cartridge (SUS) with twin electrodes; impedance phase angle correlates with protein precipitation.	Suited for single-use bag reactors; gamma-sterilizable.	FIG. 804-D-1
E-5	Laser-Diffraction Particle Cloud Analysis	Low-angle laser scattering cell in side-loop; real-time volume-weighted PSD feeds ML model to infer precipitation %.	Distinguishes protein crystals vs lipid/co-precipitates.	FIG. 805-E-1
E-6	Model Predictive Control (MPC)	30-variable state-space (temp, pH, conc, turbidity, ultrasonic, dosing rate) optimized every 5 s; constraints avoid over-dose.	Achieves ± 2 %RSD yield over 50 runs.	FIG. 806-F-1
E-7	Rule-Based Adaptive Recipe	Look-up tables (LUT) derived from Design-of-Experiments PQ; no solver.	Simple PLC implementation; validated by worst-case DOE.	FIG. 807-G-1

E-8	Machine-Learning Anomaly Guard	Gradient-boosted classifier on 10 k datapoints detects bubble/fouling outliers; auto-switches to fallback recipe.	Reduces batch aborts by 60 %.	FIG. 808-H-1
E-9	Cross-Flow Filtration ΔP Feedback	Primary control based on real-time TMP slope during constant-flux filtration (PT-501A/B).	Eliminates need for precipitation sensors; reagent dose trimmed by cake-growth rate.	FIG. 809-I-1
E-10	Amplitude-Modulated Dosing Pulses	Reagent pump PD-202 runs Duty-Cycle PWM (10 Hz) for finely metered addition; prevents local supersaturation.	Reduces micro-crystal aggregation.	FIG. 810-J-1
E-11	pH-Shift/PEG Dual-Stage Cascade	Stage-1 pH quick-shift; Stage-2 PEG metered via adaptive loop; sensors validated separately.	Increases yield of IgM fraction by 8 %.	FIG. 811-K-1
E-12	Temperature-Ramped Ethanol Fractionation	Jacket J-101 ramps from -5 °C → +10 °C while dosing; fusion model includes temperature coefficient.	Enables continuous Cohn-like cut in SUS reactor.	FIG. 812-L-1
E-13	Cloud-Supervised Twin	Edge PLC streams anonymized sensor feed to cloud digital-twin; cloud returns updated model parameters nightly.	Allows fleet-level ML improvement without on-site recalibration.	FIG. 813-M-1
E-14	Self-Testing Probe Cartridge	Optical & acoustic paths include auto-zero liquid chambers actuated by micro-valves; self-test every 30 min.	Meets FDA 21 CFR 820 automated inspection.	FIG. 814-N-1

3. Detailed Enablement of Each Embodiment

Note: Dimensions, flow-rates, sensor bandwidths, and parameter windows are given as *ranges* to satisfy enablement under 35 U.S.C. §112 while not limiting scope.

E-1 — Side-Loop Dual-Sensor Control

Hardware (XV-301, P-201, FC-301, NTU-301, US-302, PRX-303)

- 0.2-2 L min⁻¹ stainless peristaltic loop, 3/8" PTFE lines
- Flow-cell: 20 mm quartz windows; 1 MHz ultrasonic transducers

Sensors

- Turbidity: 860 nm LED, 0-4000 NTU, $t_{90} < 0.3$ s
- Ultrasonic: 2-10 MHz sweep, ± 0.05 dB cm⁻¹ resolution

Control – “Pulse-Pause-Measure” (30 s dose → 45 s mix → 15 s read); EWMA $\alpha = 0.20$; NTU & US weighted 0.5/0.5 → $\hat{P}\%$.

Calibration – 3-run PQ, gravimetric reference, proceed threshold $90 \pm 2\%$.

Cleaning – CIP 20 min @ 60 °C 1 % NaOH + 10 min 100 ppm PAA; verify NTU < 1.

Fail-safe – bubble flag if NTU \uparrow & US \downarrow > 3 σ for >5 s.

E-2 — Tri-Sensor with UV-Clarifier

Adds CF-401, UV-401 (8 s clarified slipstream every 90 s).

- UV-280 diode-array, 190-400 nm, 0.5 nm res.
 - Sensor-fusion weights: NTU 0.35 · US 0.35 · UV-280 0.30.
 - Self-check via PRX-303 baseline drift ± 0.1 %.
 - Disposable PES capsule; pressure-drop < 0.3 bar.
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3.3 Embodiment E-3 — Inline Acoustic-Resonance Probe

Hardware – Shear-mode piezoelectric resonator (38 kHz) welded into a 2-inch tri-clamp nozzle on the precipitation vessel; 316L SS enclosure; shielded coax feed-through to impedance-bridge board (RES-803).

Signal Path – The bridge excites a ± 50 ppm sweep, measures resonant-frequency shift Δf and quality factor Q at 10 Hz; linear solids range 0 – 12 % v/v with ± 0.2 % resolution.

Control Integration – Δf is Gaussian-filtered ($\sigma = 0.05$ Hz) and weighted 0.35 into the sensor-fusion estimate \hat{P} %.

Calibration – Two-point liquid standards (WFI and 5 % w/v silica) plus three-point protein-precipitate curve; auto-zero at batch start.

Cleaning / Sanitation – Probe survives SIP 30 min @ 121 °C; piezo rated 140 °C.

Fail-Safe – Δf spike > 15 Hz s^{-1} flags bubble/froth; fusion weight forced to zero until cleared.

3.4 Embodiment E-4 — Inline Dielectric-Spectroscopy Cartridge

Hardware – Gamma-sterile disposable cartridge (804-1), 6 mm ID; parallel stainless electrodes, 5 mm gap; Luer-lock ports; internal volume 4 mL.

Electronics – 100 kHz – 10 MHz sweep every 2 s; complex-permittivity ϵ^* fitted to Cole–Cole model; ϵ'' peak at ~1 MHz correlates with protein aggregation.

Control Integration – EWMA ($\alpha = 0.30$); weight 0.30 in \hat{P} %.

Calibration – Factory curve (0 %, 2 %, 6 % BSA precipitate) stored in on-board EEPROM; zero-factor self-check every slip-stream purge.

Cleaning – Single-use; dispose after batch or if impedance baseline drifts > 10 Ω .

Interlocks – Electrode-fouling $\Delta R > 10 \Omega$ triggers alarm & cartridge swap.

3.5 Embodiment E-5 — Laser-Diffraction Particle-Cloud Analysis

Hardware – 660 nm diode laser, 15 mm optical path; 30-element photodiode ring (0.1–15 °) inside a stainless flow cell.

Software / Algorithm – Mie-theory inversion → volume-weighted PSD; XGBoost regression converts $D[4,3]$ and span into $\hat{P}\%$.

Performance – Update every 5 s; fusion weight 0.25; frame rejected if PSD fit $R^2 < 0.9$.

Calibration – NIST-traceable latex beads (1, 5, 10 μm) quarterly.

Cleaning – CIP 1 % NaOH 15 min; automatic wiper cleans windows each batch.

Fail-Safe – Laser off-power or window fouling flag drops weight to zero.

3.6 Embodiment E-6 — Model-Predictive Control (MPC)

State-Space Model – 30 states (mass balances, ethanol, PEG, temp, pH, sensor lags).

Solver – Quadratic program (QP), 60 s prediction horizon, 2 s control interval; constraints: EtOH $\leq 10 \%$ v/v, pH 4.8 – 5.8, agitator ≤ 300 RPM, jacket $\Delta T \leq 3 \text{ }^\circ\text{C min}^{-1}$.

Results – 50 simulated runs: $\pm 2 \%$ RSD yield; 5 production runs: $\pm 2.3 \%$.

Fallback – Solver non-convergence > 2 cycles → automatic switch to LUT recipe (E-7) within 0.5 s.

3.7 Embodiment E-7 — Rule-Based Adaptive Recipe

Logic – 2-D look-up table (25 temp-bins \times 12 $\hat{P}\%$ -bins); output is PD-202 duty-cycle %.

Derivation – DOE: 3 temps \times 3 pH \times 3 reagent-conc; bilevel optimisation minimises over-dose.

Validation – Worst-case yield within 5 % of target; LUT retuned annually during PQ.

3.8 Embodiment E-8 — Machine-Learning Anomaly Guard

Dataset – 10 000 historical batches; features: NTU, US dB, ϵ'' , Δf , Δ TMP slope, jacket ΔT , pH drift.

Model – Gradient-boosted trees (300 trees, max depth 6), AUC 0.97.

Action – Anomaly probability > 0.8 for > 3 s \rightarrow freeze dosing, auto-run sensor self-tests, switch control to LUT (E-7).

Retraining – Continuous; edge logs anonymised & uploaded nightly (E-13).

3.9 Embodiment E-9 — Cross-Flow Filtration ΔP Feedback

Hardware – PT-501A/B 0–6 bar, 0.1 % FS; depth filter F-501 (0.65 μ m) or micro-filter cartridge.

Algorithm – Constant-flux 100 L $m^{-2} h^{-1}$; slope d TMP/ d t calculated every 10 s; target ≤ 5 kPa min^{-1} .

Recycle Logic – If slope > 5 kPa min^{-1} within first 5 min \rightarrow redirect permeate to recycle line, add 0.5 % EtOH, remix 5 min.

PQ – Hermia intermediate-blocking fit, $R^2 > 0.95$.

3.10 Embodiment E-10 — Amplitude-Modulated Dosing Pulses

PWM Parameters – 10 Hz carrier; minimum pulse 50 ms; duty-cycle 0–100 %.

Controller – PI acting on duty-cycle, integral time 20 s; prevents overshoot & micro-crystal clumping.

Anti-Chatter – If duty change < 5 % for 10 cycles, controller holds last value for 30 s.

3.11 Embodiment E-11 — pH-Shift / PEG Dual-Stage Cascade

Stage 1 (pH shift) – PD-210 doses HCl or NaOH to reach pH 5.1 (ISFET sensor $t_{90} \leq 1$ s).

Stage 2 (PEG) – PD-211 meters 8 % w/v PEG 3350 under MPC (E-6).

Outcome – IgM fraction yield +8 %; impurities –5 %.

3.12 Embodiment E-12 — Temperature-Ramped Ethanol Fractionation

Ramp Profile – Start $-5\text{ }^{\circ}\text{C}$; dose EtOH to 8 % v/v; ramp jacket to $+10\text{ }^{\circ}\text{C}$ over 20 min ($\leq 3\text{ }^{\circ}\text{C min}^{-1}$).

Model Compensation – Temperature coefficient $-0.8\text{ } \% P$ per $^{\circ}\text{C}$ applied inside fusion algorithm.

Hardware – Glycol chiller $\pm 0.1\text{ }^{\circ}\text{C}$ accuracy; jacket control valve PWM 1 Hz.

3.13 Embodiment E-13 — Cloud-Supervised Digital Twin

Edge Layer – PLC publishes 1 Hz summary frames (NTU, US, ε'' , Δf , pH, temp, $\hat{P}\%$, dosing %) by MQTT over TLS 1.3.

Cloud Layer – PyTorch LSTM predicts next-minute $\hat{P}\%$ and retrains anomaly-guard; returns updated fusion weights nightly via Update-813.

Security – Rotating keys, anonymised feature set, salted batch IDs.

3.14 Embodiment E-14 — Self-Testing Probe Cartridge

Auto-Zero Cycle – Micro-valves route WFI through optical & acoustic paths for 5 s every 30 min; controller records baseline drift.

Acceptance – Drift $> 0.5\text{ } \%$ triggers recalibration or cartridge swap; event logged to batch record.

Electronics – On-board MCU, I²C EEPROM, optical LED, piezo ping transducer; battery or 5 V rail.

Compliance – Meets FDA 21 CFR 820 (automated inspection) and ISO 13485 self-test requirements.

4. Common Hardware & Sanitation Requirements

- All wetted metal: 316L SS $\leq 0.5 \mu\text{m Ra}$; plastics: USP <88> Class VI.
- SIP exposure $\geq 20 \text{ min @ } 121 \text{ }^\circ\text{C}$ required for reusable flow cells; single-use cartridges gamma-sterilized 25 kGy.
- Maximum differential pressure ratings: FC-301 6 bar, SUS cartridge 2 bar.

5. Software Architecture

Edge PLC → Fusion Library (Rust) → Control Service (Go) → MQTT pub/sub → Cloud Digital-Twin (PyTorch)

- **Fail-safe modes** built into PLC ladder logic; cloud connection is non-blocking.

6. Critical Process Parameters (CPPs) & Operating Windows

Parameter	Nominal	Permissible	Alarm	Trip
Temperature (T-101)	$-5 \text{ }^\circ\text{C}$	$-7 \dots +2 \text{ }^\circ\text{C}$	$\pm 3 \text{ }^\circ\text{C}$	$\pm 5 \text{ }^\circ\text{C}$
pH	5.2	5.0 – 5.4	± 0.3	± 0.5
Reagent conc.	8 % v/v EtOH	$\pm 0.5 \%$	$\pm 1 \%$	$\pm 2 \%$
	$\geq 90 \%$	88 – 92 %	$< 88 \%$	$< 85 \%$

7. Validation Matrix (PQ)

Table outlines ≥ 5 lots \times 3 temps \times reagent conc. high/nominal/low for each embodiment activated; records yield, purity, TMP slope, fusion drift.

8. Fallback & Redundancy

- If sensors disagree $> 2 \sigma$ for $> 60 \text{ s}$ → freeze dosing, continue agitation, run UV-clarifier confirm.
- $\Delta\text{TMP} > 200 \text{ kPa min}^{-1}$ in first 5 min of filtration → recycle to T-101, add 0.5 % EtOH, re-measure.

9. Claims Cross-Reference

- **Claim 1** broad method (any real-time fusion signal driving adaptive dosing).
- **Claims 2-6** sensor modality sets (optical, acoustic, dielectric, spectroscopic, PSD).

- **Claims 7-10** control algorithms (MPC, LUT, PWM pulse, Δ TMP-based).
- **Claims 11-14** hardware forms (side-loop, inline probe, disposable cartridge, cloud-supervised).

10. Figure List

Comprehensive Figure List (FIG 801 – FIG 814)

Fig. #	Title	Numbered Parts
FIG 801 — Side-Loop Dual-Sensor Control	Embodiment E-1	801-1 T-101 Precipitation Tank; 801-2 XV-301 Side-Loop Isolation Valve; 801-3 P-201 Loop Pump; 801-4 FC-301 Flow Cell; 801-5 NTU-301 Turbidity Sensor; 801-6 US-302 Ultrasonic Sensor; 801-7 PRX-303 Optical Reference; 801-8 XV-302 Return Valve; 801-9 PD-202 Main Dosing Pump
FIG 802 — Tri-Sensor with UV-Clarifier	Embodiment E-2	802-1 Side-Loop Core (components of FIG 801); 802-2 XV-311 Clarifier Splitter; 802-3 CF-401 0.2 μ m Capsule; 802-4 UV-401 UV-280 Detector; 802-5 XV-312 Return/Waste Valve
FIG 803 — Inline Acoustic Resonance Probe	Embodiment E-3	803-1 Wall-Mounted Piezo Probe; 803-2 Resonance Circuit; 803-3 Interface to FUS-900
FIG 804 — Inline Dielectric Spectroscopy Cartridge	Embodiment E-4	804-1 Single-Use Cartridge Body; 804-2 Twin Electrodes; 804-3 In/Out Ports; 804-4 Impedance Chip; 804-5 Sterile Luer Locks

FIG 805 — Laser-Diffraction Particle Analyzer	Embodiment E-5	805-1 Laser Source; 805-2 Scattering Cell; 805-3 Photodiode Array; 805-4 Data Processor; 805-5 Feedback Link
FIG 806 — Model Predictive Control Architecture	Embodiment E-6	806-1 Sensor Vector; 806-2 State-Space Model; 806-3 Optimizer; 806-4 Actuator Output; 806-5 Constraint Module
FIG 807 — Rule-Based Adaptive Recipe	Embodiment E-7	807-1 PLC Ladder Logic; 807-2 Recipe LUT; 807-3 Set-Point Trim; 807-4 Alarm Block
FIG 808 — Machine-Learning Anomaly Guard	Embodiment E-8	808-1 Feature Extractor; 808-2 GBT Classifier; 808-3 Confidence Output; 808-4 Failover State Machine
FIG 809 — Cross-Flow Filtration ΔP Feedback	Embodiment E-9	809-1 PT-501A Inlet Pressure; 809-2 PT-501B Outlet Pressure; 809-3 TMP Calculation (ΔP); 809-4 XV-403 3-Way Valve; 809-5 Recycle Line
FIG 810 — PWM Dosing Pulse Modulation	Embodiment E-10	810-1 PD-202 Pump; 810-2 Duty-Cycle Controller; 810-3 FT-204 Flow Feedback; 810-4 Anti-Chatter Logic
FIG 811 — pH-Shift / PEG Dual-Stage Cascade	Embodiment E-11	811-1 PD-210 pH Pump; 811-2 PT-103 pH Sensor; 811-3 PD-211 PEG Pump; 811-4 Fusion-Control Output
FIG 812 — Temperature-Ramp	Embodiment E-12	812-1 Jacket J-101; 812-2 TIC-102 Temperature Controller; 812-3 PD-202 Ethanol Pump; 812-4 Ramp Generator

**ed Ethanol
Fractionation**

FIG 813 — Embodiment 813-1 Edge PLC; 813-2 MQTT Broker; 813-3 Cloud
Cloud-Supervised E-13 ML Server; 813-4 Update Agent
Digital Twin

FIG 814 — Embodiment 814-1 Auto-Zero Chamber; 814-2 Micro-Valves; 814-3
Self-Testing Probe E-14 Optical Test Path; 814-4 Acoustic Test Path; 814-5
Cartridge Self-Test Circuit

Brief Description of the Drawings

- **FIG. 801** is a schematic diagram of a side-loop dual-sensor control circuit used to estimate precipitation percentage in real time.
- **FIG. 802** is a schematic diagram of a tri-sensor control loop that adds an ultraviolet-clarifier branch for periodic truth-calibration.
- **FIG. 803** is a sectional view of an inline acoustic-resonance probe mounted in the precipitation vessel wall.
- **FIG. 804** is a perspective view of a disposable dielectric-spectroscopy cartridge configured for single-use flow-through analysis.
- **FIG. 805** is a block diagram of a laser-diffraction particle-cloud analyser positioned in the at-line slip-stream.
- **FIG. 806** is a functional diagram of a model-predictive control (MPC) architecture employed to modulate reagent dosing.
- **FIG. 807** is a ladder-logic chart illustrating a rule-based adaptive dosing recipe implemented on a PLC.
- **FIG. 808** is a data-flow diagram of a machine-learning anomaly-guard that detects sensor drift, bubbles, and fouling.
- **FIG. 809** is a schematic diagram of a cross-flow-filtration feedback loop that uses trans-membrane-pressure slope as a go/return decision.
- **FIG. 810** is a timing diagram depicting pulse-width-modulated (PWM) dosing of the precipitating agent.
- **FIG. 811** is a process-flow diagram of a dual-stage cascade consisting of an initial pH shift followed by polyethylene-glycol dosing.
- **FIG. 812** is a temperature-profile chart showing a controlled jacket ramp from sub-zero to positive temperatures during ethanol fractionation.
- **FIG. 813** is a network diagram of a cloud-supervised digital twin that updates sensor-fusion weights across multiple facilities.
- **FIG. 814** is a sectional view of a self-testing probe cartridge with auto-zero liquid chambers actuated by micro-valves.