Claims

1. A method of controlling a plasma protein fractionation precipitation process, comprising:

   – monitoring the precipitation in real-time with one or more in-situ analytical sensors that provide signals indicative of precipitate formation;

   – computing an estimated precipitation progress or endpoint from the sensor signals using a sensor fusion or control algorithm; and

   – adjusting the addition rate of a precipitating reagent to the process during the precipitation in response to the computed progress, thereby maintaining the precipitation within a target range or driving the process to a desired endpoint without offline assays.

2. The method of claim 1, wherein the one or more sensors include an optical turbidity sensor and an ultrasonic sensor disposed in a recirculation loop that withdraws a slip-stream from the precipitation vessel, providing at-line measurements of turbidity and sound velocity as indicators of protein aggregation (Embodiment E-1).

3. The method of claim 1, further comprising diverting a portion of the slip-stream through a micro-filter and measuring UV absorbance of the filtered sample to determine protein concentration in solution, and wherein the adjusting step is based in part on the filtered sample's absorbance (Embodiment E-2).

4. The method of claim 1, wherein the precipitation progress is monitored via an inline acoustic resonance probe mounted in the precipitation vessel, the probe's resonance frequency or damping being used to infer solution conditions related to precipitation (Embodiment E-3).

5. The method of claim 1, wherein the precipitation progress is monitored via an inline dielectric spectroscopy sensor comprising a pair of electrodes in contact with the process fluid and an impedance measurement circuit, the measured permittivity or impedance providing a signal correlated with protein precipitation (Embodiment E-4).

6. The method of claim 1, wherein the precipitation progress is monitored via a laser diffraction particle size analyzer that measures particle size distribution of precipitated solids in real time, and the adjusting step includes slowing or pausing reagent addition if the particle size distribution indicates a risk of over-precipitation or filter clogging (Embodiment E-5).

7. The method of claim 1, wherein the computing step is performed by a model-predictive control (MPC) algorithm that uses a state-space model of the precipitation process to predict future process behavior, and optimizes the reagent addition rate over a time horizon to achieve the desired precipitation endpoint while respecting process

constraints (Embodiment E-6).

8. The method of claim 1, wherein the computing step is performed by a rule-based control algorithm that follows a predefined recipe of set-points for the precipitation and dynamically adjusts those set-points based on the real-time sensor feedback, including triggering alarms or modifications to the recipe if the process deviates from expected trajectories (Embodiment E-7).

9. The method of claim 1, further comprising analyzing the sensor signals with a machine-learning anomaly detection model and, upon detecting an anomaly or out-of-bound condition in the precipitation (with confidence above a threshold), automatically transitioning the process to a safe state or fail-safe mode (Embodiment E-8).

10. The method of claim 1, wherein adjusting the addition rate of the reagent comprises applying pulse-width modulation (PWM) control to a reagent pump such that the pump is driven in pulses with a controlled duty cycle to meter small volumes of reagent with high precision (Embodiment E-10).

11. The method of claim 1, further comprising monitoring a filtration trans-membrane pressure (TMP) during a filtration step that follows the precipitation, and if the TMP or its rate of increase exceeds a predetermined limit, automatically pausing or modulating the reagent addition and/or recycling the batch flow to prevent filter fouling (Embodiment E-9).

12. The method of claim 1, wherein the process includes a two-stage reagent addition: (i) adding a first reagent to adjust solution pH to a target value, and (ii) subsequently adding a second precipitant reagent (such as polyethylene glycol) once the pH target is reached, in order to precipitate a specific protein fraction (Embodiment E-11).

13. The method of claim 1, wherein the precipitation is performed while actively controlling the temperature of the mixture according to a predefined ramp or profile (cooling or heating over time) in coordination with the reagent addition, such that temperature and reagent concentration are varied concurrently to optimize fractionation (Embodiment E-12).

14. The method of claim 1, further comprising transmitting process data to a remote server and receiving, during the same batch, updated control parameters or model adjustments from a cloud-based machine learning model that analyzes the process data, wherein the controller uses the updated parameters to refine the reagent dosing in real time (Embodiment E-13).

15. The method of claim 1, further comprising periodically diverting the process fluid or a reference fluid through a self-calibration loop that exposes the one or more sensors to a

known reference condition (e.g., a clear fluid or standard solution) and automatically adjusting sensor calibration or offset in the controller based on the sensor readings in the reference condition (Embodiment E-14).

16. A system for adaptive control of a precipitation process in biomanufacturing, comprising: at least one inline or at-line sensor providing real-time measurements of the state of a protein precipitation mixture; a reagent dosing apparatus configured to add precipitant to the mixture; and a controller operably connected to the sensor and the dosing apparatus, the controller being programmed to modulate the dosing apparatus in response to the sensor measurements so as to control the precipitation process in real time (closing the loop between measurement and addition).

17. The system of claim 16, wherein the at least one sensor includes a turbidity sensor and an ultrasonic sensor mounted in a recirculating side-loop of the precipitation vessel, the side-loop withdrawing liquid from the vessel, passing it through a flow cell that holds the turbidity and ultrasonic sensors, and returning it to the vessel (Embodiment E-1).

18. The system of claim 16, wherein the at least one sensor comprises a disposable cartridge with a dielectric spectroscopy sensor or other single-use analytical probe that can be inserted into a flow path of the process to measure a property of the mixture, the cartridge being removable and replaceable without contaminating the process (Embodiment E-4).

19. The system of claim 16, wherein the controller comprises an edge computing device at the process site and is in communication with a remote cloud server, the cloud server hosting a process model or digital twin that receives process data and sends back optimized control adjustments to the edge device, whereby the system's control strategy is refined during operation via cloud-based machine learning (Embodiment E-13).

20. The system of claim 16, further comprising a filtration unit connected to receive the output of the precipitation vessel, the filtration unit having pressure sensors to measure inlet and outlet pressure, and wherein the controller is configured to use signals from the pressure sensors to detect a filtration performance parameter (trans-membrane pressure) and to modify the operation of the dosing apparatus or process flow (including recycling flow or stopping addition) if a filtration threshold is exceeded (Embodiment E-9).

21. The system of claim 16, further comprising a self-testing sensor module including a test chamber and at least one micro-valve arranged to periodically expose the sensor to a reference fluid or empty span, wherein the controller automatically verifies sensor accuracy based on the sensor's response in the test chamber and recalibrates or generates an alarm if the response deviates from an expected value (Embodiment E-14).

22. The system of claim 16, wherein the controller is programmed with a multi-phase recipe for the precipitation process and can execute sequential control of multiple actuators, including at least one dosing pump and one or more auxiliary controls (temperature control unit, pH adjustment pump), such that different reagents or conditions are applied in stages (for example, a pH adjustment phase followed by a precipitant addition phase), all under closed-loop feedback supervision (Embodiments E-11, E-12).

23. A reagent micro-dosing apparatus for controlled addition of process reagents in a bioprocess (such as plasma protein fractionation), the apparatus comprising:

– a manifold of multiple positive-displacement micro-pumps, each pump having a pump head and rotor constructed of bioprocess-compatible materials and each pump being driven by an independent motor;

– a common injection assembly fluidly coupled to outlets of the pumps, the injection assembly having a plurality of radial nozzles that introduce reagent into a main process stream in a sterile, evenly distributed manner;

– an analytical sensor assembly positioned downstream of the injection assembly, the sensor assembly including at least one inline sensor selected from the group consisting of: a quartz crystal microbalance (QCM-D) sensor, an endotoxin detector, a dielectric or conductivity sensor, and a redox sensor, for monitoring a property of the fluid into which reagent is dispensed; and

– a control interface configured to receive control signals from a process controller and to actuate the pumps accordingly, thereby delivering specified micro-volume doses of one or more reagents into the process stream on demand.

24. The apparatus of claim 23, wherein all wetted components of the pumps, injection assembly, and sensor assembly are constructed and arranged for in-situ sterilization, including being capable of withstanding steam-in-place at ≥121 °C for at least 20 minutes without degradation (such that the entire fluid path can be sterilized as a closed loop).

25. The apparatus of claim 23, wherein the manifold is configured such that any pump can be assigned to dispense any of a set of reagents via selectable fluid connections or valves, and further comprising a flush system that, upon reassignment of a pump to a new reagent, flushes the pump and its lines with a cleaning fluid (e.g. water for injection) and verifies via the analytical sensor assembly that no cross-contamination remains (e.g. by QCM-D detection of carryover) before allowing dispensing of the new reagent.

26. The apparatus of claim 23, further comprising a memory or data storage in communication with each pump's drive, the memory storing a calibration factor or Jacobian relating changes in at least one sensor signal to the volume dispensed by that

pump, wherein the control interface or associated controller is configured to auto-learn and update said calibration factor during operation by analyzing synchronized sensor and pump data (thereby improving dose accuracy over time).

27. The apparatus of claim 23, wherein the common injection assembly includes a jacketed section and a dedicated steam loop such that the assembly can be cooled (to sub-zero temperatures) during operation and can be sterilized independently of the main process line by circulating steam through the steam loop (allowing sterilization of the injection ring between batches without affecting the main line).

28. The apparatus of claim 23, further comprising a safety interlock controller that monitors signals from one or more external quality sensors or the absence of expected control signals, and automatically pauses all pump operations if a critical condition is detected, thereby serving as a fail-safe to prevent improper dosing (for example, halting all pumps if an endotoxin level exceeds a threshold or if two consecutive sensor readings are missed).

29. The apparatus of claim 23, wherein each pump in the manifold is adapted to accept a removable pre-filled reagent cartridge attached via a sterile connector, such that the cartridge forms the pump's fluid input and can be replaced to supply a different reagent or a fresh supply without breaching sterility (optionally using gamma-irradiated disposable cartridges for each batch).

30. The apparatus of claim 23, wherein the positive-displacement micro-pumps are piezoelectric diaphragm pumps with a stroke volume less than 2 µL instead of gear pumps, while maintaining individual electronic control of each pump on a common bus (providing an alternate pump technology with similarly precise micro-dosing capability).

31. The apparatus of claim 23, wherein the control interface is further configured to perform an automated priming and self-calibration routine in which, at startup or designated intervals, a small volume of sterile fluid is dispensed through each pump and the analytical sensor assembly verifies that the baseline sensor response (e.g. frequency shift or optical absorbance) is within a predefined tolerance (indicating no residual carryover or contamination) before allowing process reagent dosing to commence.

32. The apparatus of claim 23, wherein the apparatus includes a data logging system that records, for each pump and each batch, the total run time, cumulative volume dispensed, and number of actuations, and wherein a predictive maintenance module analyzes this data to predict component wear or performance drift and generates a maintenance alert when a pump or valve is predicted to approach an out-of-tolerance condition (such as when expected dosing accuracy would exceed a threshold).

33. The apparatus of claim 23, wherein the control interface provides an industry-standard communication node (OPC-UA or equivalent) that publishes real-time dosing data and

sensor spectra, and is configured to accept recipe commands or set-points from a higher-level manufacturing execution system (MES), thereby enabling integration of the apparatus into a plant-wide control system with electronic batch reporting.

34. The apparatus of claim 23, wherein the pump manifold and injection assembly are modularly scalable, such that additional pump units can be attached and the injection assembly diameter increased to accommodate larger main process flow rates, and wherein the injection nozzle diameters or count are adjusted proportionally to maintain a target dispersion performance (e.g. constant injection CV) as the system scales up.

35. The apparatus of claim 23, further comprising a dual-ring injection system in which a first subset of the pumps (e.g. odd-numbered pumps) is connected to inject into an inner ring and a second subset of the pumps (e.g. even-numbered pumps) is connected to inject into an outer ring, the inner and outer rings delivering different types of reagents simultaneously into the process stream without mixing until in the stream (for example, enabling concurrent dosing of a hydrophobic solvent and an aqueous solution in the same time frame).

36. A non-transitory computer-readable medium storing instructions that, when executed by a processor of a precipitation control system, cause the system to perform the steps of the method of claim 1 (including monitoring the process via sensors, computing a precipitation status, and adjusting reagent addition in real time based on the sensor-derived status).