Description

Closed-Loop Citrate Anticoagulation in CRRT

Ionized Calcium Sensors (505, 506)

Introduction: Post-Filter Ca^{2+} Sensor (505): A post-filter ionized calcium sensor 505 is positioned in the extracorporeal bloodline immediately downstream of the hemofilter (i.e., in the filter effluent blood line, before any calcium is returned to the blood). Sensor 505 measures the ionized calcium concentration of blood exiting the filter, which is lowered by the citrate anticoagulant. In one embodiment, sensor 505 is a miniature **MEMS-based ion-selective electrode (ISE)** module. The sensor may comprise a solid-state calcium-selective membrane (for example, a polymer membrane doped with a Ca^{2+} ionophore) on a microfabricated electrode, combined with an integrated Ag/AgCl reference electrode. This design yields a potentiometric output (voltage) corresponding to the log of the Ca^{2+} activity. The form-factor is a small flow-through cell or cuvette that inserts into the disposable blood tubing, with minimal dead volume and a biocompatible inner surface (e.g., heparin or polymer-coated to reduce protein fouling). The sensor exhibits a near-Nernstian sensitivity to Ca^{2+} (approximately 25–30 mV per decade of concentration) with high selectivity over magnesium and potassium, and a rapid response time suitable for real-time monitoring .

Systemic Ca^{2+} Sensor (506): A systemic ionized calcium sensor 506 is placed in the return line where treated blood (after citrate filtration and calcium reinfusion) returns to the patient. In one arrangement, sensor 506 is located just downstream of the calcium infusion junction, ensuring it measures blood that has been repleted with calcium and reflects the patient's systemic ionized Ca^{2+} level. Sensors 505 and 506 are substantially similar in construction; sensor 506 may be calibrated to a higher absolute Ca^{2+} range (covering normal physiologic levels ~1.0–1.3 mmol/L) whereas sensor 505 operates in a lower range (near 0.3 mmol/L). Each sensor module is a **sterile, single-use component** with a defined wear-life (for example, 72 hours of continuous use, matching typical CRRT circuit duration).

Calibration and Drift Mitigation: Both calcium sensors 505, 506 are factory-calibrated and further calibrated in situ to ensure accuracy over the course of therapy. The system may perform a two-point calibration at initialization using known reference solutions or known plasma values: for instance, the sensor is exposed to a zero-Ca^{2+} baseline (using a calibration fluid or zero-Ca dialysate) and a standard solution (at a known 1.2 mmol/L level) to set the slope and offset. The sensors include on-board temperature sensors, and the calibration accounts for temperature and pH, ensuring the output corresponds to true ionized calcium at physiological conditions. To mitigate electrode drift over time (a known challenge with ISEs), the controller can periodically auto-zero the sensors or cross-calibrate them: e.g., pausing citrate infusion briefly and measuring systemic calcium stability, or comparing the two sensor readings when appropriate (since post-filter Ca^{2+} should rise toward systemic levels if citrate is temporarily halted). In some embodiments, a small calibration cartridge or built-in calibration fluid pathway allows flushing the sensor with calibration solution at set intervals to reset the baseline.

Additionally, the sensor's membrane and reference are designed for stability: the MEMS ion-selective electrode uses a solid contact (capacitive or conductive polymer) to minimize drift, and a double-junction reference electrode to reduce contamination. Any residual drift is corrected in software by the control algorithm, which can detect slow trend deviations and adjust the calibration offset accordingly. These measures ensure that sensors 505 and 506 provide reliable, accurate Ca^{2+} readings throughout their use, with minimal manual recalibration.

Fluidic Placement and Integration: The post-filter sensor 505 is fluidically coupled via a Luer-lock or integrally molded chamber in the hemofilter's outlet line. The systemic sensor 506 can be placed on the return line (after calcium pump infusion) or, alternatively, on a dedicated arterial line sampling port for direct patient blood measurement (in embodiments where recirculation needs to be avoided). In the preferred configuration, sensor 506 is inline on the venous return tubing but sufficiently downstream of the calcium infusion site to allow thorough mixing. Both sensors communicate their readings to the system's multi-analyte sensor bus (preferably a dual-redundant I^2C/SPI bus). Each sensor module has a unique digital address and calibration profile stored in memory, so that when a new disposable sensor is connected, the TraceLoop-MX controller board automatically recognizes it as **ionized calcium sensor type** and begins polling it at the required frequency (e.g. 1–5 Hz for real-time control). The sensor bus interface and hot-swap capability allow these sensors to be added or replaced without system firmware changes, consistent with the plug-in extensibility of the TraceLoop-MX architecture .

Citrate Infusion Pump (307) and Calcium Pump (308)

Citrate Pump 307 (Pre-Filter Infusion): A dedicated citrate infusion pump 307 meters an anticoagulant citrate solution into the bloodline *upstream* of the hemofilter (pre-filter). In **FIG. 7A**, pump 307 is connected to a citrate solution reservoir (cartridge) and injects citrate into the arterial limb of the extracorporeal circuit (e.g., via the PrismaFlex™ Pre-Blood Pump port, or an equivalent inlet on the tubing set). The citrate solution is typically an isotonic trisodium citrate (TSC) solution (for example, 4% TSC by weight, yielding ~0.105 mmol/mL citrate). Pump 307 is an electronically controlled infusion pump capable of precise mid-range flow rates: in one embodiment it is a peristaltic pump or gear pump integrated into the disposable cartridge, with an **active flow-rate envelope of about 50 to 500 mL/hour**. This range supports common CRRT blood flow rates (e.g. 100–250 mL/min) with target citrate doses of about 3–4 mmol per liter of blood . The pump's minimum controllable flow is fine-tuned (down to a few mL/hour) to allow gradual titration, and the maximum flow is hardware-limited (for safety) to a value that cannot induce unsafe citrate levels (for example, ~600 mL/h limit, corresponding to ~6 mmol/L citrate at high blood flow). Pump 307 includes an integrated flow sensor (e.g., a miniaturized thermal flow meter) providing real-time feedback of the actual citrate flow rate. This closed-loop flow monitoring (±5% accuracy) ensures the delivered citrate matches the commanded rate , and triggers an alarm if a deviation (occlusion, free-flow or pump slip) is detected. A one-way check valve is incorporated in the pump outlet to prevent backflow of blood into the citrate line, and the disposable cartridge tubing is opaque or shielded to prevent ambient light or heat from degrading the citrate solution. The citrate pump's design and software also enforce **rate-of-change limits** – for example, the control algorithm can ramp the infusion rate gradually (no more than a set increment, such as 10% per minute) to avoid abrupt shifts in blood chemistry.

Calcium Pump 308 (Post-Filter $CaCl_2$ Return): The calcium compensation pump 308 delivers a calcium chloride solution into the blood flow *post-filter*, offsetting the calcium loss and hypocalcemia induced by citrate. Pump 308 draws from a sterile calcium solution cartridge (for example, 5% $CaCl_2$ in saline) and infuses into the venous return line, downstream of the hemofilter (and downstream of sensor 505). Referring again to **FIG. 7A**, pump 308's infusion site is just before blood re-enters the patient, ensuring the infused calcium has maximal effect on systemic levels and minimizing any chance of citrate in the filter encountering undiluted calcium (which could precipitate or negate anticoagulation if introduced too early). Pump 308 is a precision infusion pump similar in form to pump 307 but optimized for lower flow rates, since the calcium solution is typically highly concentrated. An exemplary flow-rate envelope for pump 308 is **5 to 100 mL/hour** of 5% $CaCl_2$ solution. This range allows fine titration of systemic Ca^{2+}: for instance, an infusion of 20 mL/h of 5% $CaCl_2$ provides roughly 1 g of $CaCl_2$ over 5 hours, sufficient to maintain a stable systemic calcium level in typical adult CRRT settings. The pump's maximum rate can be limited to about 120 mL/h (which would correspond to an aggressive correction in extreme circumstances, but still below any rate that could acutely overload the patient with calcium). As with the citrate pump, pump 308 features an inline flow sensor and check valve. The flow sensor feedback guarantees that calcium is being delivered as intended and will alarm/stop the pump if, for example, the calcium line is occluded or the cartridge is empty. Because calcium precipitation can occur if it mixes with bicarbonate or phosphate solutions, the infusion line for pump 308 may include a short extension to ensure adequate mixing with blood and to keep the injection point separate from other fluid inputs. The pump and its controller enforce safety interlocks such that **calcium infusion ceases automatically** if the measured systemic Ca^{2+} level exceeds a high threshold (e.g. >1.3 mmol/L) or if the post-filter Ca^{2+} unexpectedly rises (which could indicate mis-timing of infusions).

Pump Control and Safety Limits: Both pumps 307 and 308 are under software control and integrate with the system's existing pump driver architecture (e.g., the PumpFlex module slots). They are equipped with **software-defined safety limits**: the controller will not command citrate pump 307 above its maximum safe flow (regardless of algorithm output), and similarly will constrain pump 308 to its safe maximum. Each pump's flow sensor provides an independent check; if a pump's actual flow exceeds the commanded rate by a significant margin (suggesting a malfunction or leak), the system will stop the pump and alarm. Likewise, if the flow rate required to maintain targets reaches a pre-set ceiling (for example, if pump 308 hits 100% for a prolonged time trying to correct Ca^{2+}, or pump 307 hits maximum attempting to anticoagulate), the system flags this condition to the operator as an out-of-range condition (potentially indicating patient-specific issues like citrate resistance or filter dysfunction). The pumps are also linked to the system's **single-fault safety states** – for example, if power is lost or a communication fault occurs, the default is to stop citrate infusion (pump 307 off) and keep calcium infusion at a maintenance drip (or off, depending on configuration), thereby favoring patient safety (avoiding continued citrate without monitoring). All these hardware and software limits ensure that pumps 307 and 308 operate only within safe bounds, significantly reducing the risk of accidental over-anticoagulation or calcium overdose.

Control Algorithm and Safety Logic (FIG. 7B)

Feedback Control Loops: The controller (e.g., a Cortex-M4 microcontroller in the TraceLoop system) executes a closed-loop control algorithm, depicted in **FIG. 7B**, to continuously regulate both post-filter and systemic ionized calcium levels. In one embodiment, two cascaded **PID**

(Proportional-Integral-Derivative) controllers are used: a first PID loop adjusts the citrate infusion rate (pump 307) based on the post-filter Ca^{2+} reading from sensor 505, and a second PID loop adjusts the calcium infusion rate (pump 308) based on the systemic Ca^{2+} reading from sensor 506. These loops operate simultaneously at a regular interval (for example, every 5 seconds, synchronized with the system's control cycle). The control targets are set such that **post-filter ionized Ca^{2+} is maintained between approximately 0.25–0.35 mmol/L and systemic ionized Ca^{2+} is maintained between about 1.0–1.2 mmol/L** . Maintaining the post-filter Ca^{2+} in this low range ensures effective regional anticoagulation (blood in the filter cannot clot due to calcium chelation), while keeping systemic Ca^{2+} in the normal physiological range prevents patient hypocalcemia and its attendant risks (e.g. arrhythmia, hypotension).

The control algorithm can incorporate **feed-forward and multi-variable logic** in addition to feedback. For example, when citrate pump 307 rate is increased, the controller anticipates a drop in systemic Ca^{2+} (since more calcium will be bound and lost) and preemptively increases pump 308 output slightly, rather than waiting for the systemic sensor to detect a decrease. Conversely, if pump 307 is slowed (or stopped), the algorithm may briefly taper down pump 308 to avoid overshooting systemic Ca^{2+}. This coordination can be achieved via a model-predictive control (MPC) scheme or a cascaded PID approach with cross-coupling terms. In some embodiments, an **MPC controller** is used in place of separate PIDs: the MPC uses a patient-circuit model (incorporating citrate pharmacokinetics and calcium distribution) to compute the optimal adjustments to both pumps 307 and 308 simultaneously. This model accounts for blood flow rate, filter efficiency, citrate metabolism (e.g. liver clearance), and current Ca^{2+} levels, and can predict future levels; the result is smoother control with fewer oscillations. Whether using PID or MPC, the controller continually adjusts the infusion rates to keep both sensor readings in range, dynamically compensating for changes such as patient metabolism shifts, therapy adjustments (e.g. changes in dialysate flow), or evolving clinical conditions.

Maintenance of Target Ranges: Under normal operating conditions, the algorithm logic is as follows. If post-filter sensor 505 reads above 0.35 mmol/L (indicating inadequate citrate anticoagulation), the controller will incrementally increase the rate of pump 307 (citrate infusion) until the post-filter Ca^{2+} falls back into range. If sensor 505 reads below 0.25 mmol/L (more citrate than necessary, approaching excessive Ca^{2+} binding), the controller will decrease pump 307 to avoid waste and to raise the filter Ca^{2+} slightly (ensuring it stays safely above the critical threshold of ~0.2 mmol/L). Meanwhile, the systemic sensor 506 drives pump 308: if the systemic Ca^{2+} falls below 1.0 mmol/L, pump 308's flow is increased to raise the patient's Ca^{2+}; if systemic Ca^{2+} exceeds ~1.2 mmol/L, pump 308 is slowed or temporarily stopped to prevent hypercalcemia. These adjustments happen in a coordinated fashion multiple times per minute, so that even as patient conditions or circuit parameters change, the target ionized calcium levels are promptly restored. The control loop has configurable gain settings (for PID: proportional, integral, derivative gains; for MPC: model parameters and cost weights) that can be tuned based on clinical experience or even adaptively adjusted. For example, the system may employ a **self-tuning PID** that gradually adapts to the patient's citrate metabolism rate—if it detects a consistent bias (e.g., requiring steadily increasing calcium infusion over time, suggesting citrate accumulation), it can adjust the controller parameters or request a clinician intervention.

Safety Logic and Alarms: The closed-loop control is backed by multiple safety overrides (see **FIG. 7B**, which illustrates the controller state diagram including normal regulation, alarm conditions, and fail-safe

states). A primary safety condition monitors the absolute Ca^{2+} levels: if at any time the post-filter ionized calcium drops below a critical threshold (for instance, 0.20 mmol/L) or the systemic ionized calcium falls below a minimum safe level (e.g., <0.8 mmol/L, which might indicate developing citrate toxicity or sensor error), the system **immediately generates an alarm** and transitions out of automatic mode. In this alarm state, the controller will **suspend citrate infusion (pump 307)** to prevent further calcium chelation, and will drive the calcium pump 308 at a maintenance rate or a slightly elevated rate to help restore systemic calcium. Simultaneously, the system can enter a fail-safe anticoagulation mode: for example, it may prompt or automatically initiate systemic heparin anticoagulation as a backup. In one embodiment, the TraceLoop controller sends a command to the CRRT machine's console (via the RS-485/CAN link) to switch the CRRT circuit to a heparin protocol (as would be done if citrate is discontinued), or it activates an onboard heparin pump (if available in one of the pump bays) to deliver heparin intravenously. The transition to heparin is represented in FIG. 7B as a state change triggered by the "Ca^{2+} low" alarm condition.

Additionally, the system monitors the **sensor health and data validity**. If either Ca^{2+} sensor 505 or 506 fails a rationality check (e.g., provides no signal, or the readings between 505 and 506 contradict expected physiology by more than a plausible range), the controller flags a sensor fault. In the event of a **sensor failure**, the closed-loop algorithm either falls back to an open-loop mode or switches to a predefined safe state. One safe mode is a **maintenance drip mode**: for example, the citrate pump 307 can be set to a low, fixed rate just enough to provide some anticoagulation (or turned off if risk of clotting is low), and the calcium pump 308 can be set to a fixed rate that was last known to maintain normal calcium – essentially holding steady until the operator can address the sensor issue. Alternatively, the system may abort citrate anticoagulation entirely on sensor failure, issue an alarm, and require clinician intervention (since accurate monitoring is no longer assured). FIG. 7B illustrates such a branch where a sensor fault or out-of-range detection leads to a "Fail-Safe Mode" state, in which citrate infusion is halted and an alarm is latched.

Hierarchy and Integration with Master Controller: This citrate control loop operates within the larger TraceLoop-MX control architecture. The system's hierarchical control layers (L-0 emergency override, L-1 guard-rails, L-2 optimizer) incorporate the citrate subsystem as follows. The citrate anticoagulation is normally managed at the L-2 optimizer level (targeting the desired Ca^{2+} ranges). However, if a higher-priority condition arises (for example, a life-threatening event detected by another sensor), the L-0 vital override layer can interrupt the citrate control. For instance, if severe hypocalcemia is detected (Ca^{2+} < 0.2 mmol/L), an L-0 rule immediately **stops pump 307 and commands appropriate countermeasures** (as described above, possibly enabling a heparin antidote or calcium bolus). Likewise, the guard-rail layer (L-1) may preemptively adjust or limit the citrate system: e.g., if the system's dose-budget watchdog predicts that continuing the current citrate rate for 30 more minutes would exceed the allowed citrate dose, the L-1 layer can throttle pump 307 in advance or alert the user . In summary, the control algorithm for pumps 307 and 308 is tightly supervised by the global safety framework—any divergence from safe operating conditions results in deterministic actions to protect the patient (audible/visible alarms, automatic pump adjustments, and fallback to manual control if needed). The state diagram of FIG. 7B encapsulates these transitions, showing normal closed-loop regulation, warning thresholds (e.g., approaching dose limits), and hard safety cut-offs that trigger system-wide responses.

Dose Tracking, EEPROM Logging, and Cartridge Lockouts

Each of the new reagent cartridges (the citrate solution cartridge for pump 307 and the calcium chloride solution cartridge for pump 308) is equipped with an **EEPROM memory chip** or similar non-volatile memory device, consistent with the TraceLoop platform's smart cartridge system . This memory stores the cartridge's identity and critical parameters, including the solution type (citrate or $CaCl_2$), concentration, and the **maximum allowable dose or volume** for that cartridge. Throughout therapy, the controller continuously tracks the cumulative amount of fluid dispensed by each pump and updates this information in two places: internally in its own logs and on the cartridge's EEPROM itself. For example, as citrate pump 307 infuses citrate into the patient's blood, an internal counter accumulates the volume (in mL) and moles of citrate delivered. Similarly, calcium pump 308's output is tallied (both volume and the equivalent mass of $CaCl_2$ or mEq of Ca^{2+}). These cumulative infusion totals are periodically written to the EEPROM on the respective cartridge (for instance, after each 50 mL or every 5 minutes, whichever occurs first) to ensure an up-to-date record that stays with the cartridge.

Dose Ceilings and Lockout: The system imposes preset dose ceilings to prevent overuse or unsafe delivery from a single cartridge. By way of example, the citrate cartridge EEPROM may specify a maximum of **3 liters of citrate solution** (approximately a full day's citrate supply in CRRT), and the calcium cartridge may have a limit of **1.0 gram of $CaCl_2$** (which corresponds to a safe upper limit of calcium replacement for the treatment session). These values are configurable based on clinical guidelines and cartridge size; once the cumulative dose recorded in the EEPROM meets or exceeds the limit, the controller will trigger a **cartridge lockout**. In a lockout state, the pump is electronically disabled from further activation, and an alert is raised to notify the operator that the cartridge is spent or the dose limit reached. For instance, if 3.0 L of citrate have been infused, the system will stop pump 307 and display an alert like "Citrate cartridge limit reached – replace cartridge." This lockout is enforced in hardware/software such that even if the cartridge is removed and reinserted, the EEPROM's stored usage prevents resetting the counter (the system reads the non-volatile record and will refuse to run the pump if the limit was already hit). This is analogous to the safety mechanism for other drug cartridges in the TraceLoop system, where **cartridges with conflicting drug-class codes or exhausted dose budgets cannot be energized** . The lockout thresholds serve both safety (avoiding excessive citrate or calcium dosing which could cause metabolic complications) and practical resource management (prompting timely replacement of fluids to ensure therapy efficacy).

Audit Logging: All events related to the citrate anticoagulation subsystem are recorded in the device's secure audit log. The TraceLoop architecture maintains an immutable ledger of real-time events , and the integration of citrate control extends this logging. Every key action – including pump rate changes, sensor readings (at regular intervals or on significant change), alarm occurrences, and any transitions to fail-safe mode – is time-stamped and stored. For example, if the post-filter Ca^{2+} dropped and triggered a safety alarm at 10:35:00, the log would record the sensor value, the alarm trigger, the automatic actions taken (pump stops, mode switch), and any user acknowledgments. The cumulative infusion totals and cartridge replacements are also logged, providing a complete dosing history. Because the audit log is tamper-resistant (events are hashed and appended securely), it supports regulatory compliance and post-treatment analysis. Clinicians or technicians can review the log to verify that the post-filter Ca^{2+} remained in range over time, how often the control algorithm adjusted the pumps, and whether any dose

limits were approached or exceeded. Moreover, if a patient experienced any adverse event or if a cartridge had to be replaced, the log offers an exact trace of what occurred and when, thereby fulfilling the **21 CFR §820.70(i) traceability requirements** for device records . The audit logging and EEPROM tracking together ensure full accountability: the former provides a system-wide chronological record, and the latter ensures each disposable cartridge carries its usage history.

Integration with the TraceLoop-MX Architecture

The closed-loop citrate anticoagulation components (sensors 505/506 and pumps 307/308) are designed as plug-in extensions of the existing TraceLoop-MX modular architecture. **FIG. 7A** can be viewed as an expansion of the system diagram to include the CRRT circuit elements. Physically, the citrate and calcium cartridges are form-factored to fit into two of the pump bays of the TraceLoop device (for example, into the PumpFlex slots 5–16 , or into dedicated CRRT interfacing bays). They interface with the common pump cradle and CAN-bus backplane , so the master controller can drive them just like any other infusion channel. When a citrate cartridge (anticoagulant class) is inserted, the system reads its EEPROM descriptor and recognizes the cartridge type and contents. This ties into the architecture's safety interlocks: the **drug-class code** on the citrate cartridge is labeled as an anticoagulant, which the system's arbiter logic will treat as mutually exclusive with any systemic anticoagulant cartridge (e.g., heparin) that might already be present . Thus, the architecture can prevent conflicting therapies – for instance, if a heparin cartridge is in use, inserting a citrate cartridge could either be locked out or trigger a prompt, ensuring only one anticoagulation method is active at a time. Similarly, the calcium replacement cartridge is identified by a unique code (e.g., electrolyte supplement class) so that the system knows it must pair with a citrate anticoagulation process; if citrate infusion is not active, the presence of a standalone calcium infusion might prompt the system to verify the use (since an unopposed calcium infusion would raise serum Ca^{2+}). In this way, the new cartridges work within the **conflict-graph arbiter** of TraceLoop to maintain therapy consistency and safety.

On the sensor side, the addition of sensors 505 and 506 leverages the multi-analyte sensor bus and hot-swap sensor module design . These sensors are simply two more nodes on the sensor network, polled by the main controller's ADC/AFE subsystem just like existing sensors (glucose, electrolytes, etc.). The TraceLoop architecture was built to accommodate new biomarkers without firmware changes , and ionized calcium sensors 505/506 exemplify this extensibility. The controller's software reads their outputs and maps them to the control algorithm described above. The sensors are also integrated into the **redundancy and fail-safe schema**: if either sensor malfunctions, the architecture's general rule of redundant sensing or default-safe input applies . For instance, although the current embodiment might have only one post-filter and one systemic Ca^{2+} sensor, the system is capable of supporting a second sensor of each type for redundancy. If dual sensors were used, any disagreement beyond 10% between two post-filter Ca^{2+} readings could automatically cause the controller to distrust those readings and fall back to a safe mode (maintenance drip) as noted in the safety logic . Even with single sensors, the system's fault detection will catch a failed sensor and act accordingly, as described. The **safety states** of the overall device (which may include general alarm state, safe-mode state, or critical failure state) now incorporate specific responses for the citrate subsystem. For example, the system's *critical alarm state* may be triggered if post-filter $Ca^{2+} < 0.2$ mmol/L for more than a few seconds, which would propagate a

global alarm, stop pump 307, and might also signal the CRRT console (via the external link) to pause blood flow until the issue is resolved.

Finally, the closed-loop citrate control is harmonized with the **TraceLoop supervisory software** that manages multi-analyte homeostasis. This means the citrate anticoagulation loop does not operate in isolation, but in concert with other therapeutic loops. The system's hierarchical arbiter will prioritize life-critical actions: for instance, if the patient's blood chemistry triggers a higher-priority intervention (such as calcium is dangerously low, which is directly within this loop's domain, or another critical event like hyperkalemia requiring immediate treatment), the arbiter can override or adjust the citrate control commands (L-0 override might *stop citrate infusion* as an offending infusion in the face of severe hypocalcemia). Conversely, during normal operation, the citrate control will function as an L-2 optimizer process that quietly maintains Ca^{2+} levels in the background. **FIG. 7B** (controller state diagram) illustrates how the system transitions between these control states: it shows, for example, a normal closed-loop regulation state; a transition to a "Guard Rail" state if nearing dose limits (where the system may alert the clinician or modulate the setpoints to stretch cartridge life); and a transition to an "Override/Alarm" state if a safety threshold is breached, where the higher-level safety logic takes control (which could include switching anticoagulation strategy). Because the TraceLoop-MX platform supports external device coordination (e.g., ventilators, pumps, CRRT machines) , the integration of this citrate subsystem can also involve commanding the CRRT device. In some embodiments, the TraceLoop controller not only controls its own pumps 307/308, but can also instruct the CRRT machine's native pumps or settings – for instance, adjusting the dialysate flow rate or turning off the CRRT machine's anticoagulant setting – via a communication interface. This ensures there is no conflict between the external machine's settings and the TraceLoop-managed infusions.

In summary, the novel closed-loop citrate anticoagulation process is fully enabled within the TraceLoop-MX architecture: the hardware (sensors and pumps) plug into existing buses and slots, the firmware recognizes and manages them with the established safety and logging infrastructure, and the control algorithms operate under the same hierarchical and fault-tolerant principles that govern all TraceLoop therapeutic loops. This integrated design allows an advanced CRRT anticoagulation method to be added to the system without compromising its single-fault tolerance or extensibility, thereby expanding the system's capabilities to maintain circuit patency and patient safety during continuous renal replacement therapy.

Figures: *FIG. 7A* schematically illustrates the CRRT closed-loop citrate anticoagulation subsystem, including blood filter, citrate pump 307 pre-filter, post-filter Ca^{2+} sensor 505, calcium pump 308 for post-filter $CaCl_2$ infusion, and systemic Ca^{2+} sensor 506 on the return line. *FIG. 7B* is a state diagram of the control algorithm and safety interlocks for this subsystem, showing normal operation (closed-loop control of pumps 307, 308), alarm conditions (e.g., Ca^{2+} below threshold triggering pump shutdowns and alarms), and integration points where control transitions to or from higher-level system states (such as fallback to heparin anticoagulation or system-level overrides). The depicted flow in FIG. 7B includes the detection of sensor faults and the corresponding safe-state logic, ensuring that the invention's control method is robust against failures and consistent with the overall TraceLoop safety framework.

Below are re-written figure call-outs that focus exclusively on the novel sensor and hardware elements of the citrate-anticoagulation subsystem. They replace the earlier FIGs 7C-7F with hardware-centric illustrations and legends.

FIG. 7C — MEMS Inline Ion-Selective Calcium Sensor (505 / 506) – Cross-Section & Signal Path

A cut-away drawing shows the flow-through cuvette (purple), solid-state Ca^{2+}-selective membrane (yellow), on-chip Ag/AgCl reference (grey) and integrated Pt temperature sensor (red). Arrows trace whole-blood entry and exit, while a flex-cable carries the high-impedance voltage and SPI temperature data to the sensor bus.

Ref. No.	Component	Unique Advantage
① Membrane	Polymer doped with Ca-ionophore X	Near-Nernst 25-30 mV/decade slope
② Solid-contact layer	PEDOT:PSS conductive polymer	Eliminates liquid inner fill ⇒ drift ↓
③ Reference electrode	Double-junction Ag/AgCl	72 h stability in protein-rich blood
④ Micro-heater / Pt RTD	Trim-flashes at 37 °C	Auto-temp compensation < ±0.02 mmol L^{-1}
⑤ Luer-lock shell	One-twist sterile install	Sensor hot-swaps without circuit break

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FIG. 7D — Dual Micro-Pump Cartridge (307 & 308) with On-Board Flow-Meter & EEPROM

Isometric rendering of the snap-in disposable shows two coaxial gear pumps, each capped by its reagent pouch. An internal MEMS thermal mass-flow die ⑥ reads real-time flow; an I^2C EEPROM ⑦ stores cartridge ID, concentration and cumulative mL. Mechanical keys ⑧ prevent citrate and $CaCl_2$ pouches from swapping bays.

Ref. No.	Feature	Novelty
⑥ MEMS flow die	±5 % inline verification—no bulky Coriolis sensor	
⑦ EEPROM + CRC	Dose ledger survives power loss; lockout bit hardware-enforced	
⑧ Bay keying	Physically blocks reagent mix-ups	

FIG. 7E — Hot-Swap Sensor-Bus Topology & Address-Negotiation Handshake

A simplified bus diagram shows up to 32 smart sensors on dual-redundant I^2C lines. When a new 505/506 module is inserted, it: (1) pulls BUS_DETECT low; (2) broadcasts its 16-bit part-type; (3) awaits a 7-bit runtime address from the master; (4) streams calibrated Ca^{2+} value at 250 ms intervals. Bus-level watchdogs drop any sensor silent for > 1 s, driving the arbitration engine into maintenance-drip mode.

Stage	Time-Budget	Hardware Safeguard
Detect pulse	< 1 ms	Pull-up resistors ensure line recover if sensor dies

Address grant	3 ms	Master verifies no address collision
First data frame	10 ms	CRC-8 appended for silent corruption detection

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FIG. 7F — PumpFlex Bay – Mechanical & Electrical Interlocks

Section view of the modular PumpFlex chassis: spring-loaded pogo pins deliver power/data; optical tag ⑨ confirms reagent class via coloured fiducial; latching cam ⑩ mates only if cartridge firmware passes a class-conflict check sent over the backplane. Hall-effect sensor ⑪ detects motor rotation independently of the gear encoder, enabling single-fault detection of runaway pumps.

Ref. No.	Hardware Interlock	Purpose
⑨ Optical tag	Stops “heparin” cartridge from occupying citrate bay	
⑩ Latching cam	Ensures positive occlusion—no partial seating	
⑪ Hall sensor	Secondary RPM check → auto-stop on > 10 % speed error	

These four redesigned figures spotlight the MEMS calcium sensor architecture, the dual reagent-pump cartridge, the hot-swap sensor bus, and the mechanical/electrical interlocks that collectively constitute the novel hardware platform underpinning the closed-loop citrate anticoagulation subsystem.