Cadence™

VIRUS INACTIVATION (VI) SYSTEM

The Cadence™ single-use VI system (Fig 1) is a fully automated system for batch and continuous processing. It performs low pH virus inactivation to an incoming elution stream continuously, with minimal operator involvement. The system collects the elution stream from a continuous chromatography system. However, it can easily process as a standalone system or with a batch chromatography system.

The system automates sequentially: eluate collection, pH decrease, hold at low pH, pH neutralization, and transfer to the next unit operation.

The system consists of a control unit that attaches to one or two system-specific Allegro™ single-use mixers dependent on the application. The specification of the flow kits currently supports 24-hours continuous operation.

The Cadence VI system offers the following benefits:

- Designed for integrated unit operation.
- Fully automated for true continuous processing.
- Reduced risk of operator error.
- Ability to operate in batch or continuous mode for flexible facility fit.

Fig 1. Cadence VI system.

System overview

Low pH virus inactivation has historically relied on labor-intensive, manual procedures. The Cadence VI system automates this established methodology, streamlining the process. As bioprocessing advances toward greater unit operation integration and parallel continuous processing, the implementation of automated systems becomes imperative – offering reduced operator error and enhanced reproducibility.

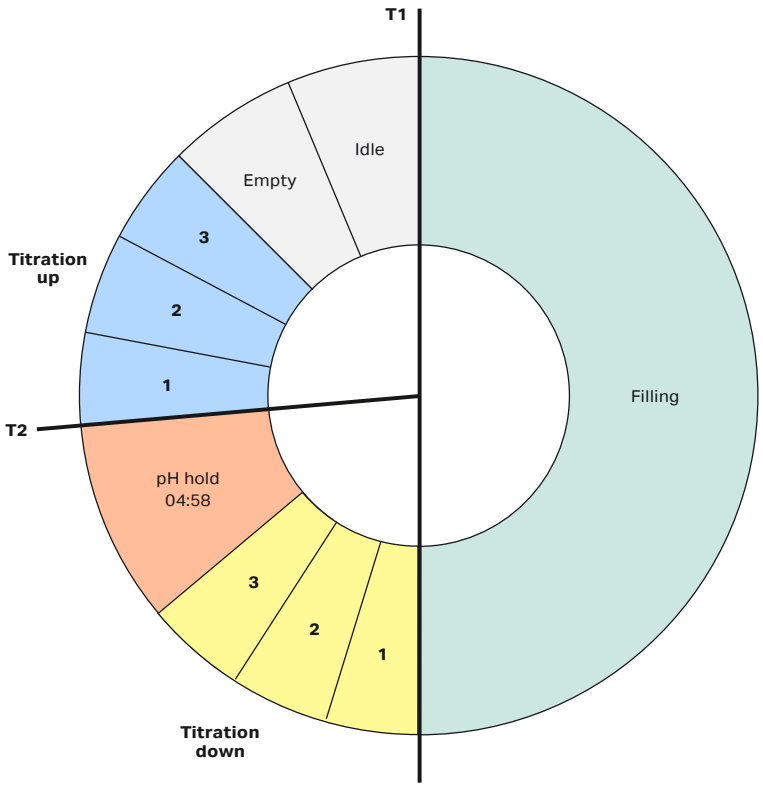

Fig 2. A circular process status graphic shows the system state at a glance.

Fig 3. Home screen of the software.

Software

The software represents the latest generation of our automation philosophy. We carefully design and test all interactions and workflows to minimize operator error and ensure easy interaction with the system (Fig 2 and 3).

The program comes with built-in sequences for both batch and continuous operation, which can be fully configurable to meet all process requirements.

The system includes an Open Platform Communications (OPC) server to easily connect it with other units, and with supervisory control and data acquisition (SCADA) systems.

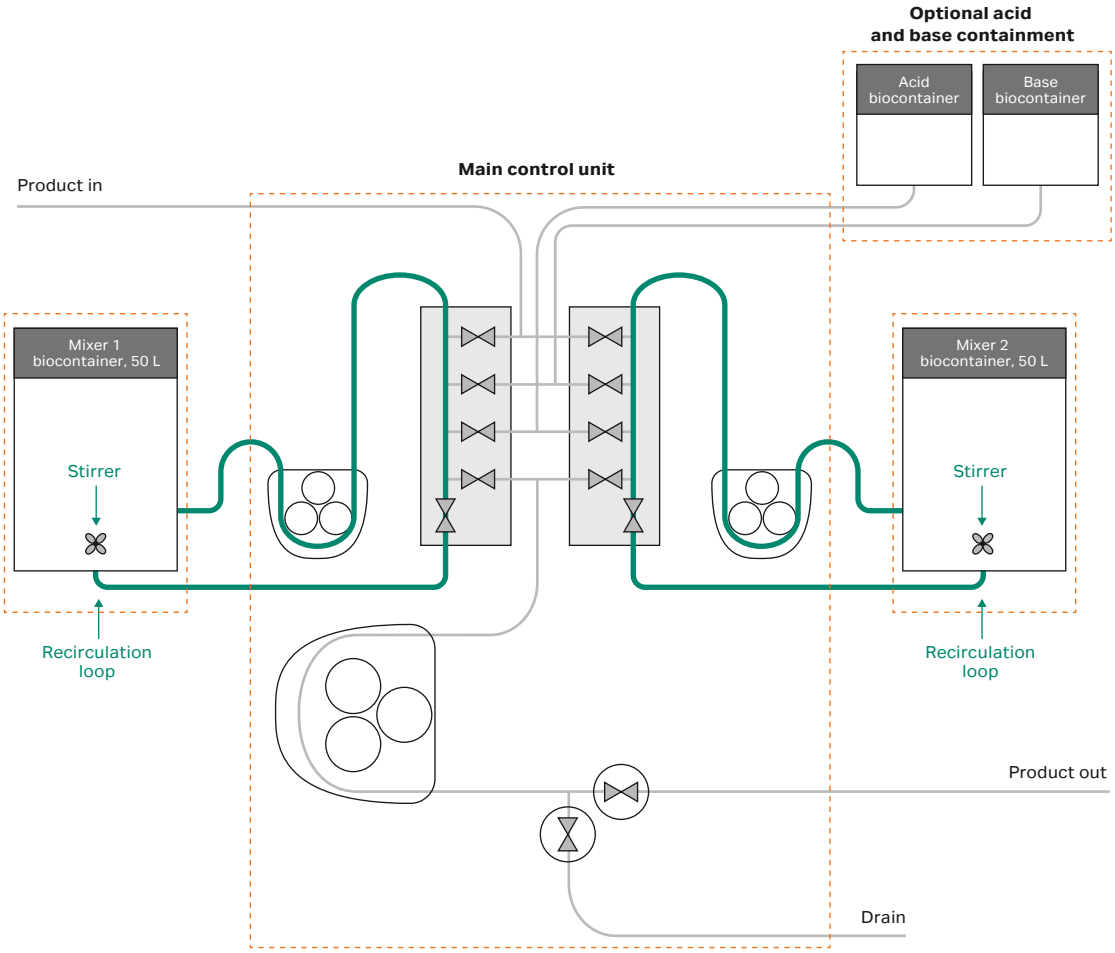

Fig 4. Schematic of the Cadence VI system.

Mode of operation

Recirculation loop

The fluid flow into and out of the mixer is via the bottom of the unit, using the recirculation loop (Fig 4).

The recirculation loop facilitates:

- Entry of externally-pumped elutions into the mixer.
- Addition of acid and base.
- Transfer out of treated elution pool after processing.
- Mixing of the elution pool during titrations and hold.
- Sampling of elution pool.

The gentle manner of liquid addition from the bottom of the mixer, combined with close control of the impeller by the control unit, allows the transfer, titration and mixing of the elution pool without foaming and splash back. This minimizes the risk of carry-over between batches of elution.

Two-mixer operation

The system mimics the traditional approach of manual low pH virus inactivation. The collection, low pH titration down, hold, and high pH titration are all performed in the same mixer.

During continuous operation, when the system has reached steady state, the incoming elution flow is collected into one mixer, while the second mixer processes the collected elutions.

When mixer #2 has finished processing and has transferred out the current treated elution pool, it is then available for receiving elutions. Mixer #1 can then begin treating the next batch of elutions while the elution stream is directed to mixer #2. The diversion of the flow between mixers can be set to be switched when a certain fill level has been reached, or alternatively when connected to the continuous chromatography system at the end of the current elution after a certain minimum volume has been collected.

The valve-block (Fig 5) provides an effectively zero dead-leg valve configuration which ensures that the entire elution pool in the mixer and recirculation loop is effectively mixed and exposed to the inactivation cycle.

Single-mixer operation

The system can operate with only one mixer attached, facilitating batch operations. A dedicated method template is included within the software to allow easy configuration.

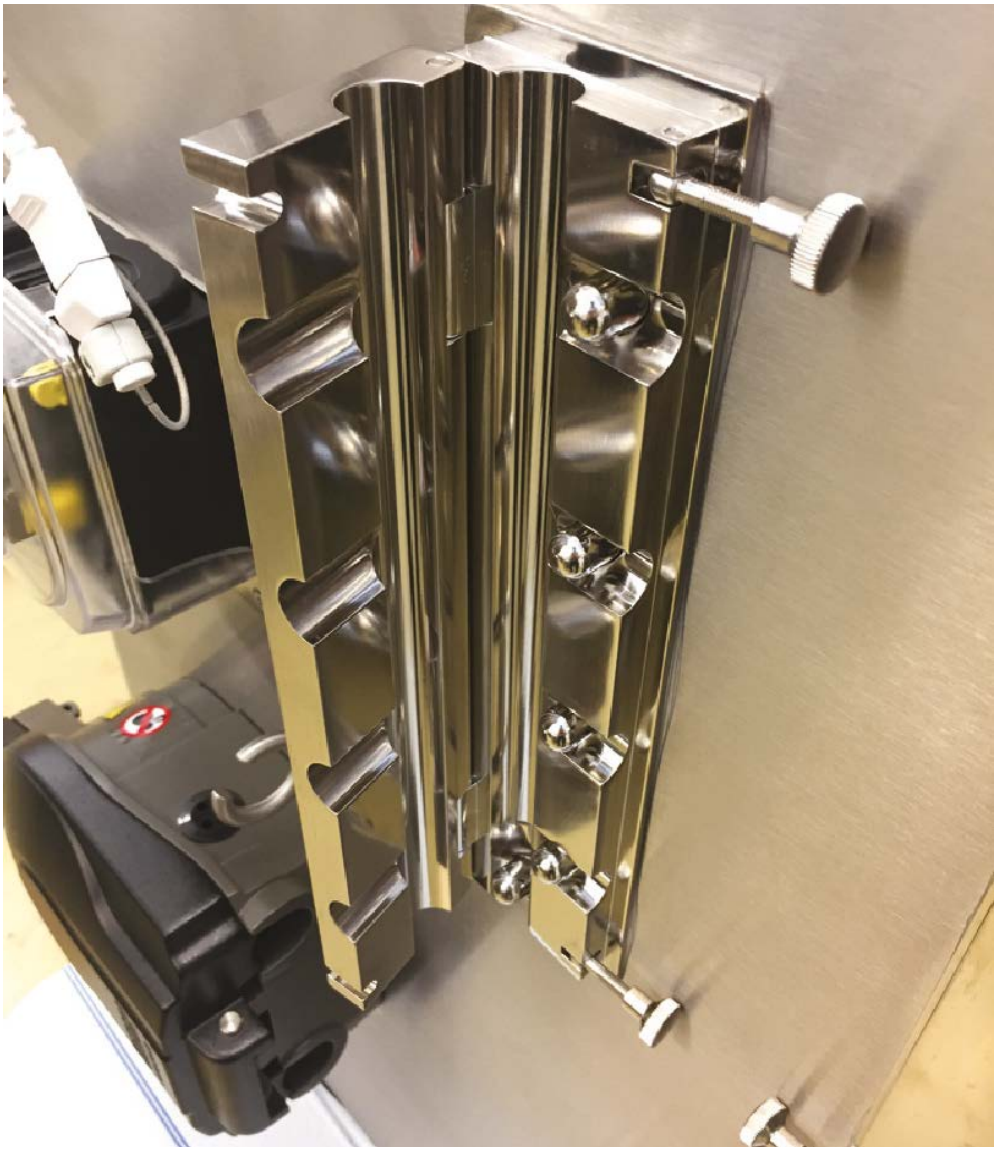

Fig 5. One of the two valve-blocks, opened, displaying the interior, into which the single-use liner from the separate flow kit is fitted. The vertical line represents part of the circulation loop. This configuration enables minimal hold up volume.

pH titrations

To ensure time-efficient operation, the titrations are based on a decreasing dosing volume system (Fig 6).

An initial large dose is added to make a quick step change in pH to get close to the desired set point, and subsequently medium-sized doses are added until an intermediate set point is reached. To obtain the final pH set point, the titration process adds small doses, mixes, and checks the pH until the final set point is reached.

The use of the decreasing dose methodology ensures that the risk of overshoot is minimized, while processing in a timely manner.

For both acid and base additions, the titrations are fully configurable to ensure that the process can be optimized for a particular application.

We can supply onsite support with a subject-matter specialist to ensure that configuration and integration with your process is as easy as possible.

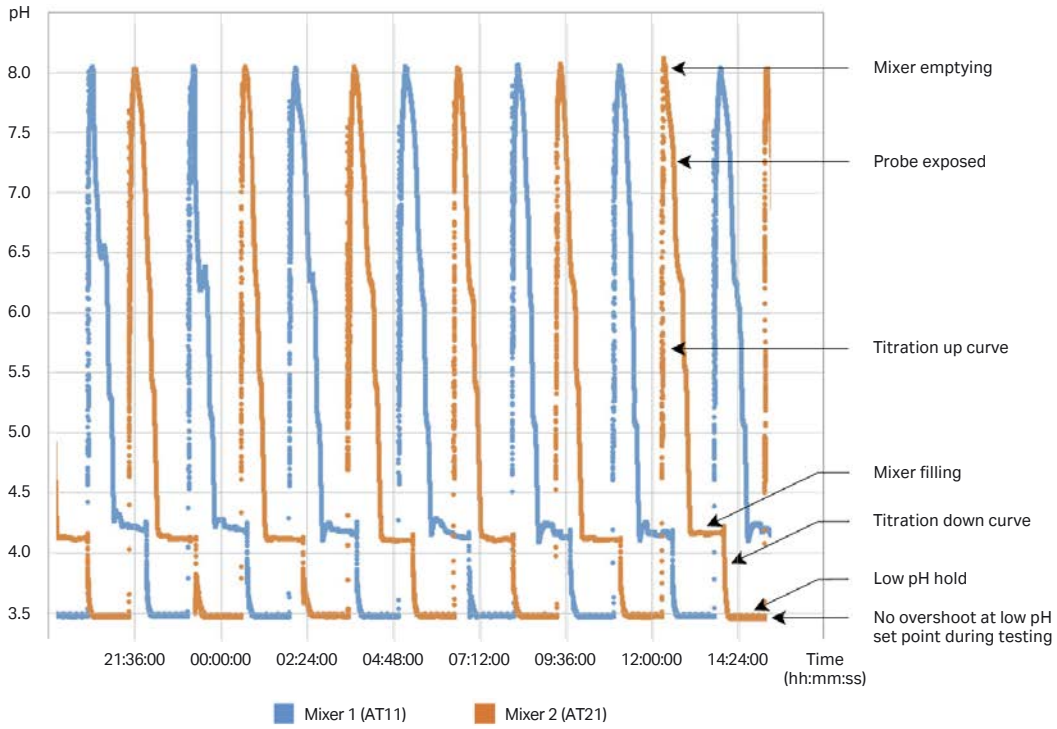

Fig 6. pH graph showing steady-state titrations to low pH and high pH set points.

Performance

The Cadence VI system can process elutions at a rate of up to approximately 30 L/h. The flow rate that the system can accommodate is dependent on titration behaviors, incubation time, and other upstream process conditions.

To put this into context, for a typical monoclonal antibody (mAb) process, Table 1 shows a guideline operating envelope for the Cadence VI system with 50 L Allegro single-use mixers.

Please contact us for help with detailed capacity determination.

Table 1. A guideline operating envelope for the Cadence VI system

	Titer 1 g/L				Titer 5 g/L				Titer 10 g/L			
	Bioreactor size (L)											
	200	500	1000	2000	200	500	1000	2000	200	500	1000	2000
6 hours	In range	In range	In range	In range	In range	In range	Not in range	Not in range	In range	Not in range	Not in range	Not in range
24 hours	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	Not in range

Flow kit installation

The flow kits are designed to be installed in less than 30 minutes. They are color-coded to ensure that the installation is correct the first time. An on-screen installation guide leads you through the process. We developed the process through user testing to ensure simple installation, saving time and minimizing operator error.

System specifications

Dimensions main control unit (w × d × h)	1100 × 900 × 2005 mm without warning light; 1100 × 900 × 2225 mm with warning light
Dimensions Allegro mixer (w × d × h)	964 × 654 × 1364 mm
Weight	350 kg (main control unit); 155 kg (Allegro mixer, full); 105 kg (Allegro mixer, empty)
Number of mixer positions	Two (two required for continuous operation, one required for batch operation)
Maximum operating pressure	0.4 barg single-use assembly (atmospheric pressure only in mixer biocontainer)
Air supply	6 barg (main control unit feeds air to the mixers)
Electricity supply	Single phase

Cadence VI single-use (SU) flow kit

Item	Description
Hose and connectors	All tubing is silicone, with CPC connectors internally and sanitary clamp connectors to interface with upstream and downstream processes
Pressure	PendoTECH pressure transmitter
Recirculation pump	Insert is standard silicone tubing-rated for 24 hours operation
Transfer pump	
Gamma irradiation dose	25 to 50 kGy
Tube size	¼ in., ⅜ in., ½ in.

Process-wetted materials of construction

Material*	Claims and compliances
Silicone	USP <88> Class VI, USP <87>, 21CFR177, latex-, phthalate-, and melamine-free
Polypropylene (PP)	USP <88> Class VI, 21CFR177, latex-, phthalate-, and melamine-free
Polysulfone (PSU)	USP <88> Class VI, ISO 10993, USP <661>, USP <381>, latex-, phthalate-, and melamine-free
Polycarbonate (PC)	USP <88> Class VI, ISO 10993, USP <661>, latex-, phthalate-, and melamine-free

*All components are either ADIF or EMA/410/01 compliant

Component specifications

Dosage/recirculation pumps	Peristaltic pump	Flow range 150 mL/min – 2400 mL/min (at 10% - 90%)
Transfer pump	Peristaltic pump	Flow range 2 L/min – 8 L/min (at 20%-80%)
Valves	Pinch valves	Single pinch valves (outlet) and pinch valve block
Pressure measurement	Single-use sensor	Range: -0.48 bar to 5.2 bar Accuracy of sensor: +/-2% in the range 0 to 0.41 bar +/-3% in the range 0.41 to 2.07 bar +/-5% in the range 2.07 to 4.14 bar Accuracy of transmitter 0.1% of full scale
pH measurement	Reusable probe	Range: 0-12 Accuracy of sensor: ± 0,02 pH; Accuracy of transmitter: ± 0,03 pH
Weighing platform	Load cell	0 to 60kg (+/- 20g)

All accuracies according to supplier datasheet

Continuous operation and expiry

Continuous operation	Specification of the flow kits supports 24 hours continuous operation
Expiry	Flow kits carry a minimum shelf life of 24 months

Ordering information

Description	Product code
VI - Control system complete with two pH probes (CE version)	CADVISYS1CE
VI - Control system complete with two pH probes (UL version)	CADVISYS1UL
VI - Allegro 50 L mixer VI specific (CE version)	CADVIMIX50LGRCE
VI - Allegro 50 L mixer VI specific (UL version)	CADVIMIX50LGRUL

Cadence VI single-use flow kits

The Cadence VI system comprises four separate flow kits:

- A flow kit to interconnect with the upstream elution source
- The control panel flow kit
- Two identical mixer biocontainer flow kits

The flow kits are supplied double-bagged and gamma-irradiated.

Description	Product code
VI – flow kit for the control system (includes interconnection flow kit and control system flow kit), one required	VICAD-CT-1
VI – Allegro 50 L mixer biocontainer VI specific, no pH probe, two required to complete the system	VICAD-MX-50
pH probe, two required per system, reusable probes. First set supplied with the control system	LGRMX225PH
pH probe installation bellows, two required per system	639-80N

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