

ÄKTA pcc™

CHROMATOGRAPHY SYSTEMS

ÄKTA pcc™ chromatography system is developed for purification of target proteins in continuous downstream processes using periodic countercurrent chromatography (PCC) at process development scale. The technology employs three or four chromatography columns to create a continuous purification step. In a PCC setup, columns are switched between the loading and non-loading steps such as wash and elution. Continuous chromatography supports process intensification by reducing footprint and improving productivity. In addition, continuous chromatography is especially suited to the purification of unstable molecules, as the short process time helps ensure stability of your target product.

Key benefits of ÄKTA pcc system include:

- Dynamic control functionality to automatically adjust for variations in resin binding capacity, differences in column volume, or changes in feed composition
- Real-time monitoring of process performance through trend curves for UV, amount of target molecule in elution peaks, and sample volume loaded on each column per cycle
- PCC method design tool to support transition from batch to continuous processing
- Flow compensation capabilities to adjust for changing conditions in connected steps upstream or downstream of the continuous chromatography step
- Extensive UV capabilities to cover a broad feed range
- Method templates to support use of the system in both bind-elute and flow-through mode

General system description

ÄKTA pcc system is based on the well-established ÄKTA™ platform of chromatography systems designed to simplify system interaction and operational handling. The system consists of the ÄKTA pcc instrument and UNICORN™ system control software. The instrument offers easy access to working areas using a swivel foot, and has a modular design, with all valves, monitors, and columns mounted on the wet side of the instrument. The wet side allows easy interaction with the system, and has a door and pump cover for safer handling during runs (Fig 2). A buffer tray on top of the instrument provides a large storage area for vessels



Fig 1. ÄKTA pcc chromatography system.



Fig 2. The wet side of ÄKTA pcc system allows easy interaction with the system.

and bottles. On the front side of the instrument, ÄKTA pcc system has a built-in, cooled fraction collector that provides secure product storage. A display on the front panel informs you of the current instrument and method state and, together with the process picture displayed on the system control computer, allows you to easily monitor and control your runs.

Principles of PCC

Compared with batch operations, continuous chromatography can offer:

- Productivity gains through increased utilization of chromatography resin binding capacity
- Reduced footprint of system, buffer, and columns through increased production capacity
- Continuous bioprocessing by integration of upstream and downstream unit operations
- Process robustness and control by steady-state operation
- Reduced process time and less hold steps, for example, to ensure stability of delicate target molecules

In PCC, keeping two columns in the loading zone allows for overloading of the first column without the risk of product loss, as the breakthrough will be caught by the second column (Fig 3).

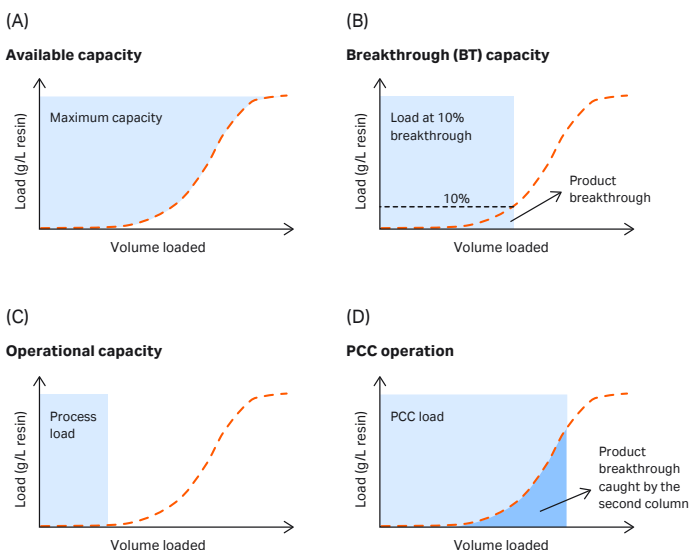


Fig 3. Capacity utilization for batch capture chromatography vs PCC. (A) Total available capacity of a chromatography resin. (B) The capacity typically measured during process development experiments. (C) The capacity typically utilized in manufacturing after adding safety factors. (D) Example of capacity utilized when implementing PCC. Note that product breakthrough is captured by the next column in the loading zone.

ÄKTA pcc can be used in a three-column (3C) or four-column (4C) PCC setup. The 3C PCC setup features two parallel flows: one for loading of two columns in the loading zone and one for the non-loading steps, for example, elution and regeneration of the third column (Fig 4). The steps are designed to align with the column position being eluted.

In step 1, columns 2 and 3 are in the loading zone. Column 2 can be overloaded without sample loss, as column 3 catches the breakthrough from column 2. In this way, the utilization of the resin binding capacity is maximized. Column 1 is in the parallel flowpath for elution and regeneration.

In step 2, the overloaded column 2 is switched out of the loading zone. Column 3 becomes the first column and column 1 becomes the second column in the loading zone. The overloaded column 2 will now be subjected to the non-loading steps, such as elution and regeneration in the parallel workflow.

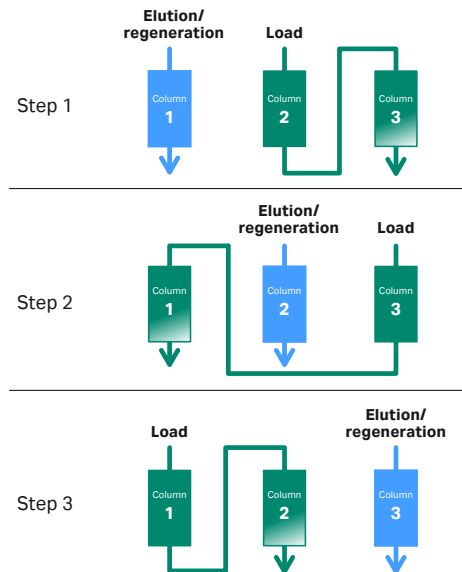


Fig 4. Principle of 3C PCC workflow.

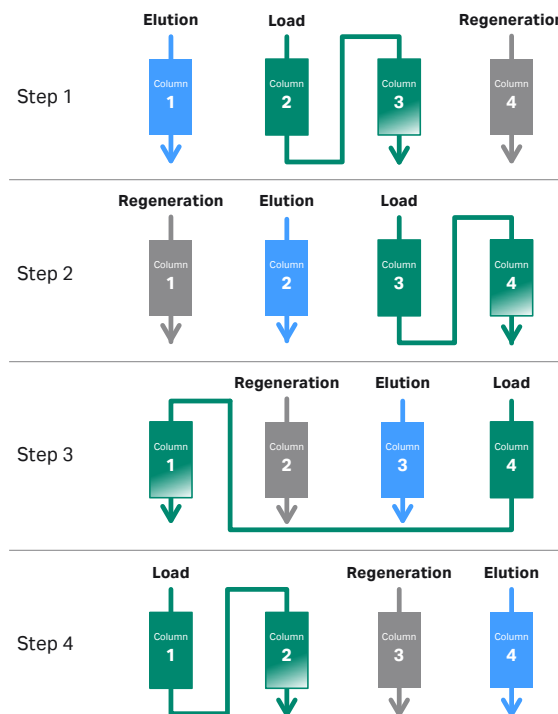


Fig 5. Principle of 4C PCC workflow.

In step 3, the overloaded column 3 is switched out of the loading zone. Now, column 1 becomes the first column and column 2 the second column in the loading zone, while column 3 is subjected to elution and regeneration in the parallel workflow. These three steps are repeated in a cyclic manner until required sample volume is reached (or until resin lifetime is expended and the column needs to be repacked or exchanged).

The 4C PCC setup employs the same principle as the 3C PCC setup. However, as the non-loading steps can become limiting in a 3C PCC setup (Fig 4), these steps can be split on two columns and run in parallel utilizing a third flow path in the 4C PCC setup (Fig 5). A 4C PCC setup allows for balancing the loading and non-loading steps.

Dynamic control

One of the key features of ÄKTA pcc system is the dynamic control function, in which UV detectors are used to monitor and dynamically control the switching of columns at a predefined level of sample breakthrough. The ability to control the column loading automatically makes the system highly responsive to variability in the product stream, as can be the case with perfusion cell culturing, or in column performance (e.g., compensation for loss of resin binding capacity, differences in bed volume between columns or in sample concentration over time). The principle of dynamic control is based on the relative difference in UV signals before and after the first column in the loading zone at breakthrough.

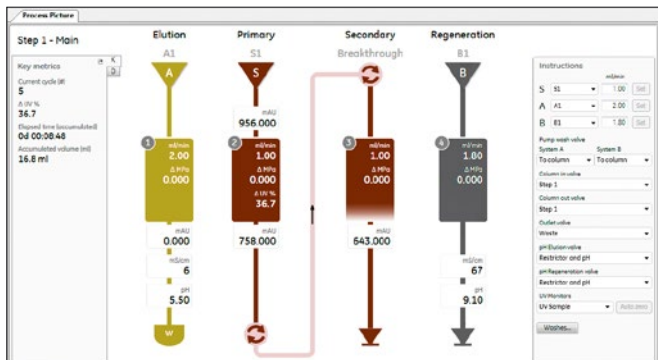


Fig 6. Process picture for the 4C PCC system setup.

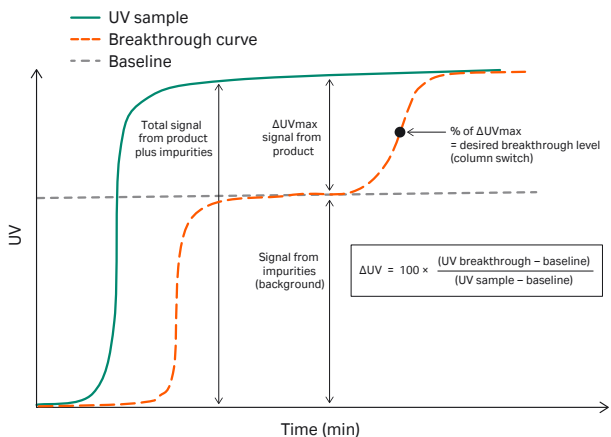


Fig 7. Overview of the two-step breakthrough, displaying the central UV signals used for dynamic control by the ÄKTA pcc system.

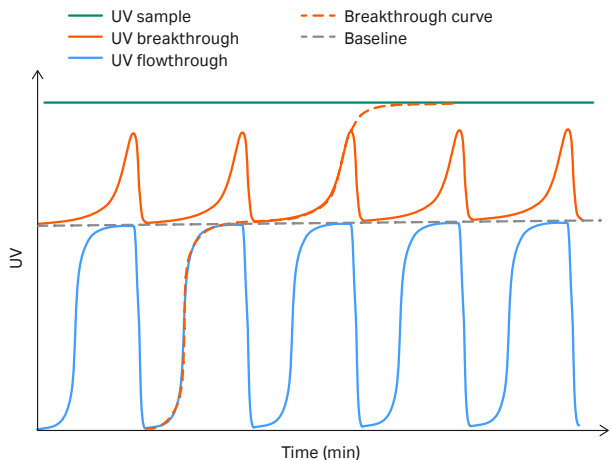


Fig 8. UV signal detectors used for dynamic control by ÄKTA pcc system.

A schematic overview of the flow path of ÄKTA pcc system is shown in the process picture in Figure 6. The difference between the baseline UV and the UV signal at 100% breakthrough for a fully loaded column is defined as ΔUVmax (Fig 7). The level of breakthrough is defined as percentage of ΔUVmax, where the desired level is process-dependent. The ÄKTA pcc system uses UV detectors assigned to the process stream and not to the separate columns. Hence, each breakthrough curve is generated based on signals from two UV detectors (Fig 8).

Trend curves

Real-time monitoring of process performance through trend curves provides an additional level of control of the continuous runs. Trending during runs is available for UV, amount of target molecule in elution peaks, and sample volume loaded on each column in each cycle.

PCC method design tool

Included with the ÄKTA pcc system is a PCC method design tool that supports transition from batch to continuous processing (Fig 9). Using a batch mode breakthrough curve, the tool enables you to theoretically vary your parameters to reach an optimal purification step based on your criteria. The method can, for example, be optimized for productivity or process time. Note that the PCC method design tool is a model and suggested process parameters need to be verified through actual laboratory runs.

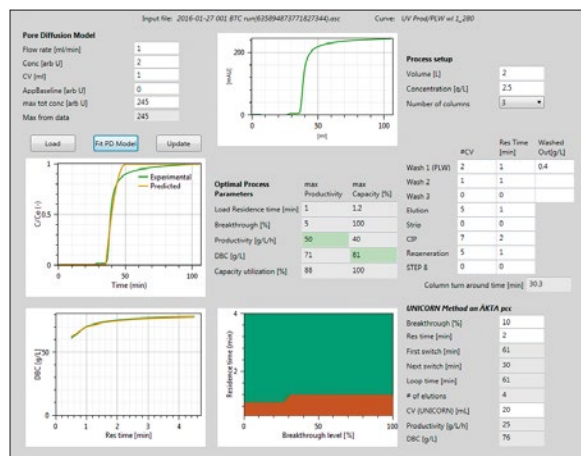


Fig 9. PCC method design tool.

Dynamic flow compensation

ÄKTA pcc system is equipped with the possibility to dynamically adjust the flow rate for the continuous chromatography step performed on the system. This is useful when the system is connected to additional unit operations either upstream or downstream of the ÄKTA pcc system. The dynamic flow compensation will allow you to adjust the flow rate with a percentage value to compensate for changes in the connected process steps.

Post-load wash

When the first column in the loading zone has reached its breakthrough level, there is a risk of losing unbound product if changing the flow path to the drain position during wash of the overloaded column. As shown in Figure 10, this loss can be minimized by performing a post-load wash of the overloaded column into the regenerated column before adding the regenerated column to the loading zone.

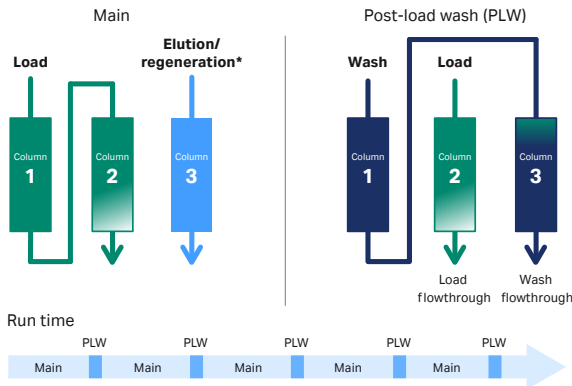


Fig 10. Post-load wash minimizes product loss during the wash step.

* Includes wash, elution, strip, CIP, re-equilibration.

UV capabilities

Monitors and sensors are included in all flow paths to keep control of your chromatography run (Fig 11). ÄKTA pcc system features extensive UV capabilities, including three UV LEDs (280 nm), of which two are used for dynamic control and one triple wave-length UV for detection of elution peaks. The UV flow cell is available in path lengths of 5.0, 2.0, and 0.4 mm to support dynamic control of a broader feed range.

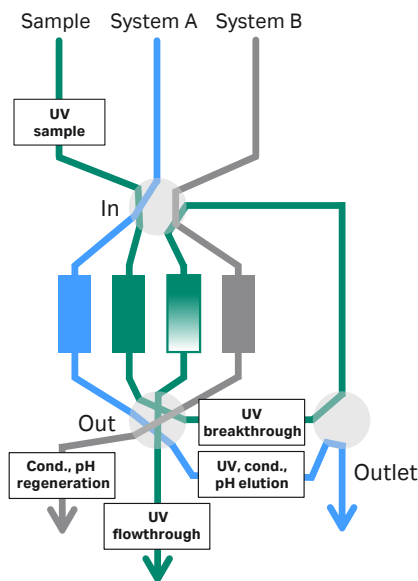


Fig 11. Positioning of monitors and sensors in the flow path of the ÄKTA pcc system.

For example, the 0.4 mm flow cell covers samples with higher titers and background signals from the cell culture feed, as it lowers the absorbance level to be within the linear range of the detector and therefore gives reliable delta UV measurements (Fig 12).

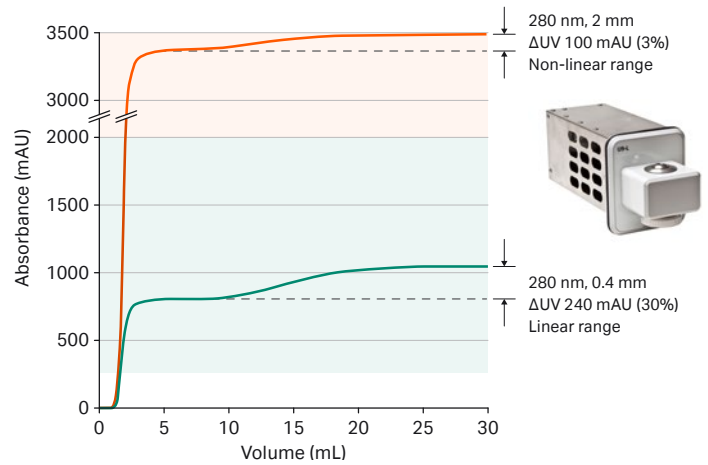


Fig 12. Different UV path lengths to cover a broader feed range.

UNICORN system control software

The well-established UNICORN software gives you real-time control of your chromatography system and includes valuable tools for increasing operational security, efficiency, and productivity. To learn more about the different features of the UNICORN software, please refer to our data file CY12681.

Application support

Included with the ÄKTA pcc system are method templates to support different applications. The templates provide a starting position that can be adjusted to your specific needs. Templates for both bind-elute and flow-through applications and for 3C PCC and 4C PCC setups are available.

Application examples

Continuous chromatography in downstream processing of a monoclonal antibody

PCC and straight-through processing (STP) technologies were evaluated in a continuous three-step monoclonal antibody (mAb) purification process. Antibody capture was performed using MabSelect™ SuRe LX protein A chromatography resin in a 3C PCC setup on the ÄKTA pcc system. To assess robustness of the setup, 10 cycles were performed. The results showed consistent yield and purity over time. Using the 3C PCC setup, the capacity utilization could be increased by 56% as compared with an equivalent batch run for the mAb purified.

The capture step was followed by two polishing steps in an STP setup on the ÄKTA pure™ chromatography system. Using continuous chromatography, the results show similar yield and purity as can be expected when the individual unit operations are run in batch mode, while increasing utilization of the chromatography resin capacity. This eliminates the need for intermediate hold-up tanks, and reduces equipment footprint.

For additional information, see our application note CY13649.

Dynamic control to adjust for variable feed concentration

To show the ability of the dynamic control functionality of ÄKTA pcc system to adjust for changes in feed titers, an experiment was set up in which the feed was altered between

two different mAb concentrations. As shown in Figure 13, the dynamic control functionality of ÄKTA pcc system was able to adjust for the difference in feed concentration during the run. As can be seen for the breakthrough signal (Fig 13A), the time, UV absorbance level, and steepness of the UV curve change as the mAb concentration is changed between 1.8 and 1.5 mg/mL. Still, breakthrough is consistently maintained at the defined ΔUV (Fig 13A) by the dynamic control functionality, and the difference in concentration is reflected only in the time before the breakthrough occurs. Consistency in sample load can be seen in the low variation in the amount of eluted mAb, with relative variations of less than 3% (Fig 13B).

For additional information, see our application note CY15112 and reference 1.

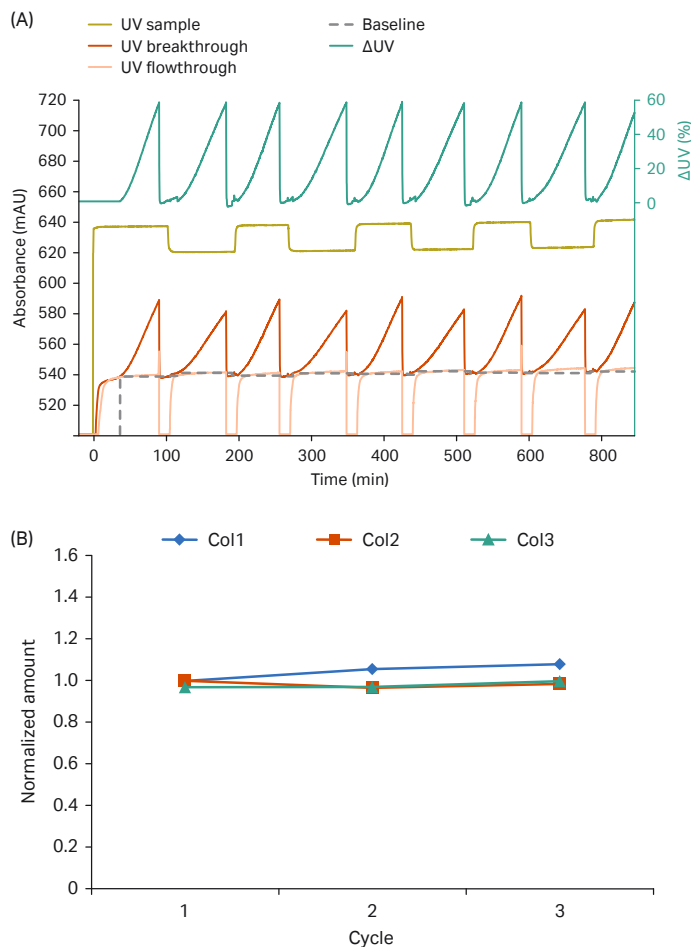


Fig 13. (A) Switching between feed concentrations of 1.5 and 1.8 mg mAb/L during load onto a MabSelect SuRe LX column at a 2.5 min residence time. (B) Amount of eluted mAb per column (Col1 to Col3) when switching between feed concentrations of 1.5 and 1.8 mg mAb/L during load onto MabSelect SuRe LX resin at a 2.5 min residence time.

Dynamic control to adjust for variations in chromatography resin capacity

A decrease in resin binding capacity can occur over time. Variations in resin binding capacity can also be due to differences in resin volume between packed column beds. To mimic such a situation, an ÄKTA pcc system equipped with one MabSelect SuRe column (Col1) and two MabSelect SuRe LX columns (Col2 and Col3) was used in a 3C PCC setup to show the system's ability to adjust for changes in column performance (Fig 14).

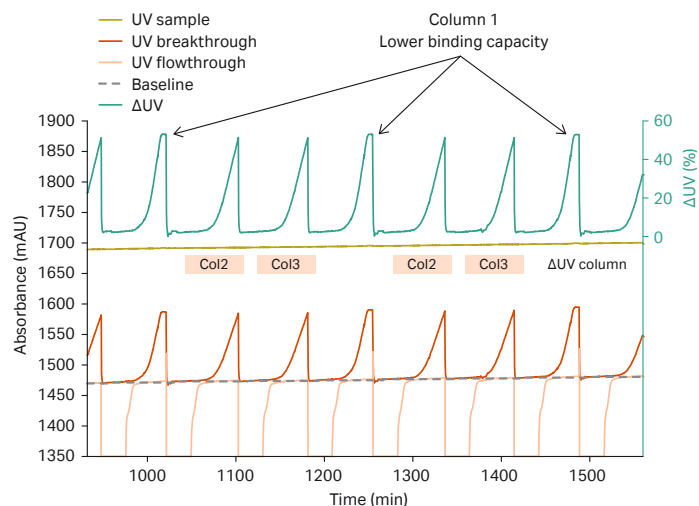


Fig 14. Difference in dynamic binding capacity (DBC) between MabSelect SuRe (Col1) and MabSelect SuRe LX (Col2 and Col3) resins at 5 min residence time for a mAb concentration of 4.5 g/L. MabSelect SuRe resin reaches the set ΔUV faster than MabSelect SuRe LX resin, shown as the ΔUV signal plateau occurring every third load (arrows).

MabSelect SuRe resin has lower DBC compared with MabSelect SuRe LX resin. The system detects the lower DBC of Col1 (MabSelect SuRe) as the breakthrough occurs earlier on this column. The dynamic control functionality was able to adjust for the difference in resin DBC between the columns. Despite the difference in DBC between the resins, the relative variance with regard to the amount eluted mAb per column was less than 3%.

For additional information, see our application note CY15112.

Advances in protein A chromatography have led to newer resins, including MabSelect Prisma™, MabSelect Prisma X, and MabSelect SuRe 70 resins.

Integration of continuous upstream and downstream operations in mAb production

Process intensification is a strategy to reduce production costs, while improving product quality and throughput in the manufacturing of biopharmaceuticals. For a competitive production process, continuous or semi-continuous upstream and downstream processing can be employed. In a study, the integration of a high-performing upstream cell culture process with downstream purification utilizing emerging technologies such as PCC and STP was demonstrated. The developed mAb production and purification process, performed in a continuous manner, showed a performance equivalent to traditional processing performed in batch runs, while adding the benefits of reduced equipment footprint and eliminated need for intermediate hold-up steps.

For additional information, see our poster CY14323.

Another example of a semi-continuous process is described in our application note CY14069. Here, a demonstration of how different unit operations in a laboratory-scale mAb process can be connected and integrated into a semi-continuous process is described. In brief, the mAb process consists of perfusion cell culture, continuous capture chromatography, viral inactivation (VI), post VI filtration, batch polishing chromatography, and a final pH adjustment step (Fig 15).

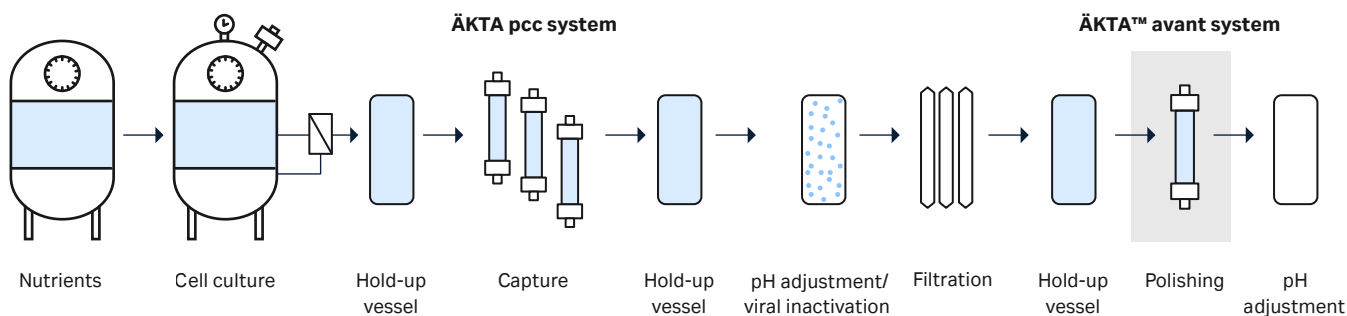


Fig 15. Schematic overview of the connected and integrated process, with hold-up vessels placed between the different unit operations.

Proven process scale-up

Our offering of process-scale PCC systems allows for scaling of the continuous chromatography process (Fig 16). Customized process-scale systems are available on request.



Fig 16. Cytiva's scalable PCC solutions. The manufacturing scale systems are available with stainless steel (SS) piping.

Related products

Protein A affinity chromatography resins

We offer a wide range of MabSelect affinity resins for capture of mAbs, antibody fragments, multispecific antibodies, biosimilars, and similar molecules. The specific properties of the ligand and resin bead, such as the mass transfer rate and binding capacity, must be evaluated when used in a continuous process together with the target molecule and feed conditions.

Chromatography columns

We offer a variety of chromatography columns for use in PCC setups, such as the small-scale HiTrap™ and HiPrep™ prepacked columns and the larger-scale HiScale™ and AxiChrom™ columns. Recommended column sizes range from 1 mL columns to columns with inner diameters (ID) of 50 mm and bed heights of up to 10 cm.

System specifications

System configuration	Benchtop system, external computer
Control system	UNICORN 7 or later version
Connection between PC and instrument	Ethernet
Dimensions (W × H × D)	860 × 660 × 710 mm
Weight (excluding computer)	119 kg
Power supply	100 to 240 V~, 50 to 60 Hz
Power consumption	800 VA
Enclosure protective class	IP 21, wet side IP 22
Tubing and connectors	
Inlet	PTFE tubing, 2.9 mm ID, 5/16–24 UNF connections
Pump to outlet valve	PEEK tubing, 1.00 mm ID, 10–32 UNF connections
Environmental ranges	
Storage and transport temperature	-25°C to 60°C max 48 h outside operating temp range
Chemical environment	See user manual
Operating ranges	
Temperature	4 to 35°C
Relative humidity	20 to 95%, non-condensing

Technical specifications

Pumps

Pump type	Piston pump, metering type
Flow rate setting	0.01 to 75 mL/min
Pressure range	0 to 2 MPa (290 psi)
Viscosity range	0.7 to 10 cP
Flow-rate specifications	
Conditions	1.0 to 75 mL/min, 0.8 to 2 cP
Accuracy	± 1.5%
Precision	RSD < 0.5%

Mixer

Mixing principle	Chamber with a magnetic stirrer (three-column configuration)
Mixer volume	1.4 mL 5 mL 15 mL (accessory)

Note: 15 mL mixer chamber can be added on request. Mixer applicable for three-column configuration only

Gradient formation

Gradient flow rate range	Binary: 1 to 75 mL/min (three-column configuration)
Gradient composition accuracy	Binary: ± 0.5%

Note: gradient formation functions available for three-column configuration only.

Valves

Type	Rotary valves
Functions	Inlet A, Inlet B, Inlet sample, Pump wash, Column, pH, Outlet

Number of inlets

Inlet A	8
Inlet B	8
Inlet sample	8

Pressure sensors

Placement of sensors	Before and after columns
Range	0 to 2 MPa (290 psi)
Accuracy	± 0.015 MPa or ± 1.5%, whichever is greater

Air sensors

Placement	Inlet A, Inlet B, Inlet sample
Optional placement	After sample pump
Sensing principle	Ultrasonic

Elution UV monitor

Placement	After elution column
Wavelength range	190 to 700 nm in steps of 1 nm, up to three wavelengths simultaneously
Absorbance range	-6 to 6 AU
Linearity	within ± 2% at 0 to 2 AU
Operating pressure	0 to 2 MPa (290 psi)
Flow cells	2 mm optical path length, 2 µL cell volume 0.5 mm optical path length, 1 µL cell volume (accessory) 10 mm optical path length, 8 µL cell volume (accessory)

Note: 0.5 and 10 mm UV cell can be added to the quote on request

UV LED

Placement	Before first column in the loading zone (UV sample), between first and second column in the loading zone (UV breakthrough), and after the second column in the loading zone (UV flowthrough) column (three- and four-column configurations). After regeneration column (UV regeneration) optional in four-column configuration).
Wavelength range	Fixed 280 nm
Absorbance range	-6 to 6 AU
Linearity	280 nm: within ± 5% at 0 to 2 AU
Operating pressure	0 to 2 MPa (290 psi)
Flow cells	2 mm optical path length 0.4 mm optical path length, 17 nL cell volume (accessory) 5 mm optical path length, 20 µL cell volume (accessory)

Note: 0.4 and 1 mm UV cell can be added on request

Technical specifications (continued)

Conductivity monitor

Placement	
After elution column	Three- and four-column configuration
After regeneration column	Four- and six-column configuration
Conductivity reading range	0.01 to 999.99 mS/cm
Accuracy	± 0.01 mS/cm or ± 2%, whichever is greater (within 0.3 to 300 mS/cm)
Operating pressure	0 to 2 MPa (290 psi)
Flow cell volume	22 µL

Temperature monitor

Placement	
After elution column	Three- and four-column configuration
After regeneration column	Four-column configuration
Reading range	0 to 99°C
Accuracy	± 1.5°C within 4 to 45°C

pH monitor

Placement	
After elution column	Three- and four-column configuration
After regeneration column	Four-column configuration
pH reading range	0 to 14
Accuracy	± 0.1 pH unit (within pH 2 to 12) Temperature within 3°C from calibration temperature
Operating pressure	0 to 0.5 MPa (72 psi)
Flow cell volume	129 µL

Outlet valve fractionation

Placement	After elution column
Number of outlets	8
Delay volume (UV to outlet valve)	535 µL

Fraction collector

Placement	After elution column
Number of fractions	up to 576
Vessel types	3, 8, 15, or 50 mL tubes
Deep-well plates	96, 48, and 24
Bottles	250 mL
Vessel type selection	Automatic recognition
Fraction volumes	1 to 250 mL
Spillage-free modes	Accumulator
Protection of fractions	Covered vessels and climate control (settable 6 to 20°C)
Organic solvents	No
Delay volume (UV to dispenser head)	1807 µL

Ordering information

System and software	Product code
ÅKTA pcc system	29218598
UNICORN 7 WrkStn pure-BP-exp	29702890
UNICORN 7 Remote	29702882
UNICORN 7 Dry	29702884
UNICORN 7 Manufacturing package	29708935
UNICORN 7 StdAlon Evaluation	29702886
UNICORN 7 Evaluation Classic	29702888

A range of computers, monitors, keyboards, printers, and cables are available, for details please contact us.

Optional components

Valves	
Versatile valve V9H-V	29090691
Sensors	
UV monitor U9-L	29011360
Note: Flow cells are ordered on separate product code	
UV flow cell 2 mm for U9-L	29011325
UV flow cell 5 mm for U9-L	18112824
UV flow cell U9-0.5, 0.5 mm for U9-M	28979386
UV flow cell U9-2, 2 mm for U9-M	28979380
UV flow cell U9-10, 10 mm for U9-M	28956378
Air sensor L9-1.2 mm (1)	28956502
Air sensor L9-1.5 mm (1)	28956500
Adapter for air sensor	28956342

Note: The 1.5 mm air sensor is placed before the inlet valves for the A, B, and sample inlets; the position for the 1.2 mm air sensor is before the column in valve.

I/O Box E9

I/O Box E9	29011361
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Real-time unit

Real-time unit	29285868
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Accessories

Cassettes	
Cassette tray, holds up to 6 cassettes	28954209
Cassette, holds 6 × 50 mL tubes (2-pack)	28956402
Cassette, holds 15 × 15 mL tubes (2-pack)	28956404
Cassette, holds 24 × 8 mL tubes (2-pack)	28956425
Cassette, holds 40 × 3 mL tubes (2-pack)	28956427
Cassette, holds 40 × 5 mL tubes (2-pack)	29133422
Cassette, holds one 96-, 48-, or 24-well deep-well plate (2-pack)	28954212
Rack, holds 55 × 50 mL tubes	28980319
Rack, holds 18 × 250 mL bottles	28981873

Ordering information (continued)

Holders	Product code
Column holder	28956282
Column holder rod	28956270
Column clamp OD 10 to 21 mm	28956319
Tubing holder, spool, for inlet tubing	29014283
Tubing holder, comb	28956286
Bottle holder	28956327
Flexible column holder	28956295
Multi-purpose holder	29011349
Rail extension	29011352
Extension box	29110806

OD = outer diameter

Related content and products

	Literature code
Application note: Continuous chromatography in downstream processing of a monoclonal antibody	CY13649
Application note: The use of dynamic control in periodic counter-current chromatography	CY15112
Application note: Integrated semi-continuous process for mAb production	CY14069
Poster: Use of a continuous chromatography system for both resin screening and scale-up studies	CY14405
Data file: UNICORN 7 control software	CY12681
Explore protein A resins	Link

Reference

1. Chmielowski *et al.* Definition and dynamic control of a continuous chromatography process independent of cell culture titer and impurities. *JChromatogr* 2017;A 1526:58–69. doi:org/10.1016/j.chroma.2017.10.030.

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