ÄKTAcrossflow filtration system

FILTRATION HARDWARE

The automated ÄKTAcrossflow™ tangential flow filtration (also called cross flow) system is intended for process development and optimization as well as for small-scale processing of material for laboratory or preclinical applications. Installed with the UNICORN™ control software, the ÄKTAcrossflow system puts you in control of your filtration process to allow consistent simulation of large-scale conditions and provide data for comprehensive analysis of results.

The benefits of working with the ÄKTAcrossflow system include:

- Support of a broad range of both ultrafiltration and microfiltration applications, covering filter areas from 16 cm^2 to 1200 cm^2
- Flexible operation using either hollow fiber filter cartridges or filter cassettes, with additional instructions that enable normal flow filtration operations
- Thorough and efficient process development with full transmembrane pressure (TMP) and flux scouting
- The same familiar UNICORN interface as for ÄKTA™ chromatography systems
- Low shear force pumps that prevent disruption of proteins or cells and require no cooling
- Minimum working volumes as low as 25 mL

Note: achievable minimum working volume is dependant on filter and tubing kit size.

System design and description

The compact ÄKTAcrossflow bench-top system is suitable for installation in laboratories (Fig 1). The UNICORN software installed on a separate computer is needed to control the system and can be used in a manner that complies with current Good Manufacturing Practices (cGMP). The system is easy to sanitize and suitable for use in cleanroom environments.

Fig 1. ÄKTAcrossflow system has a compact design and is easy to sanitize.

The system is built with ÄKTA system components for reliability, scalability, and flexibility. The ÄKTAcrossflow system is delivered with UV, pH, and conductivity detectors, as well as air, pressure, and temperature sensors. The valves and the fittings are specially developed for hygienic, leak-free operation. Electrically actuated diaphragm valves diminish hold-up volumes and prevent dead volumes.

The system is suitable for use with a wide range of cross flow filtration devices, including Cytiva's hollow fiber filter cartridges, for cell harvest/concentration and product concentration/diafiltration. The ÄKTAcrossflow system is designed to operate filters with areas up to 1200 cm^2 and is suitable for processing small sample volumes.

The UNICORN control software allows quick and simple communication between the system and the user. The software also meets the stringent control and data handling procedures required in modern laboratory and production facilities. The ***Method Wizard*** provides easy method generation. Optimized methods can be transferred from laboratory to production scale.

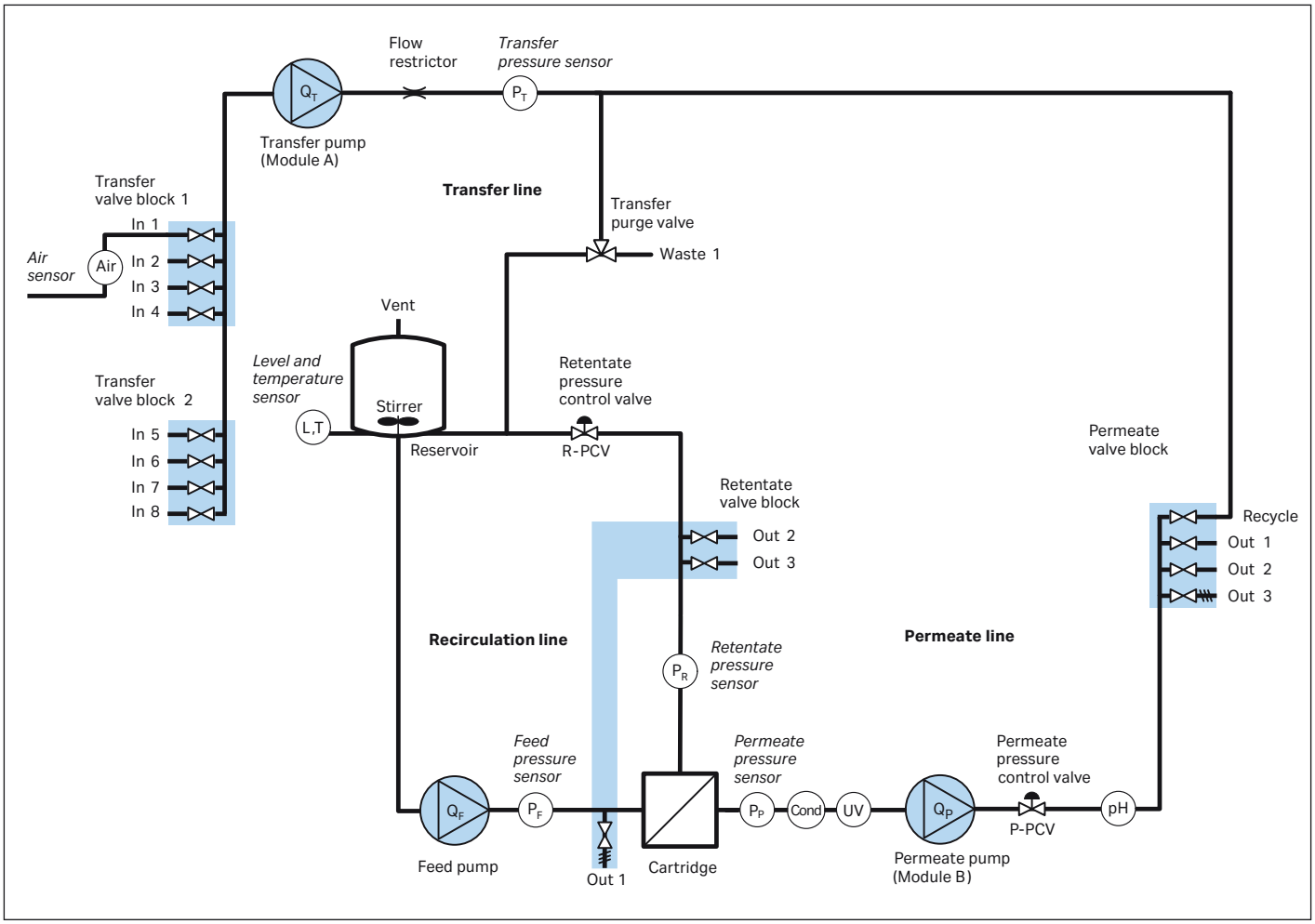

Fig 2. The system flow path.

Flow path

Figure 2 shows the ÄKTAcrossflow flow path, including a transfer line, recirculation line, permeate line, a reservoir, as well as the valves and pumps (Fig 3). The flow path components and sensors are easy to sanitize and are described in more detail below.

Transfer line

The transfer valve blocks allow for selection of the appropriate inlet tubing among eight different inlets for sample, buffers, cleaning-in-place (CIP) solutions, rinse solution, and storage solution. The transfer pump delivers liquid to the reservoir. Like all pumps of the ÄKTAcrossflow system, the transfer pump is a high-precision metering pump that acts as a flow meter by reporting accurate flow rate and volume information to the UNICORN control software. The transfer purge valve allows for rinsing of the transfer lines. A pressure sensor (P_T) measures the pressure in the transfer line as a safety precaution. An air sensor can be used on the sample inlet tubing to allow for efficient loading of the sample.

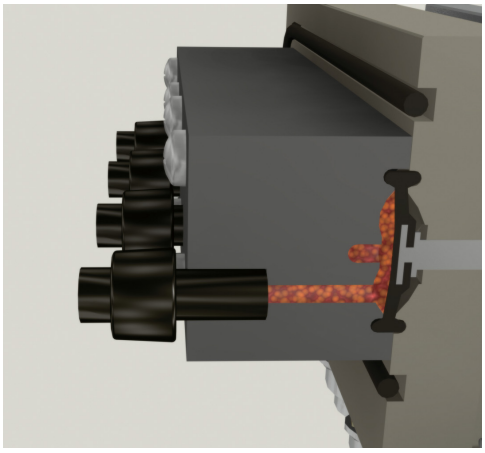

Fig 3. Sanitary membrane valve.

The reservoir

The reservoir contains the sample and the retentate stream (liquid rejected by the filter). A magnetic stirrer in the bottom of the reservoir ensures uniform mixing between the bulk fluid, the retentate, and any liquid added via the transfer line during constant volume operations. An integrated level (L) sensor at the bottom of the reservoir is used for constant volume operations and to protect the filter against introduction of air by detecting and activating an alarm on an empty reservoir during concentration and diafiltration operations. A temperature sensor (T) is incorporated with the level sensor and constantly reports the temperature of the liquid fed into the filter device.

Recirculation line

The feed pump creates the necessary cross flow over the membrane by operating at either constant feed flow, retentate flow, feed pressure, delta pressure, or shear rate (for hollow fiber filters). The retentate valve block comprises three outlets, one pre- and two post-filter, and is used primarily for product recovery. The pre-filter outlet (R-VB-Out1) allows for liquid removal at high flow rates. Feed pressure (P_F) is measured at the inlet of the filter cartridge. At the retentate side of the cartridge, a pressure sensor (P_R) measures the pressure of the liquid rejected by the filter. Figure 4 shows the retentate pressure control valve (R-PCV) that is used during TMP process control.

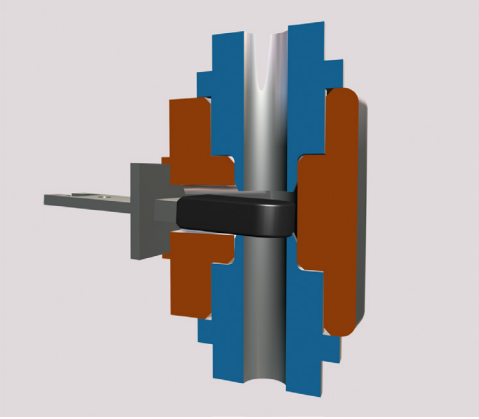

Fig 4. Retentate pressure control valve.

Permeate line

At the permeate side of the cartridge, sensors monitor permeate pressure (P_P), conductivity (Cond), UV absorbance (UV), and pH (pH). A permeate pump is an integral part of the permeate flow path. During TMP process control, the flow rate of the pump is regulated by the UNICORN software to match the permeate flow from the filter and continuously report the permeate flow rate, thereby acting as a flow meter. For microfiltration applications, the permeate flux is kept at a constant rate. A pressure control valve (P-PCV) is situated after the permeate pump to ensure flow rate accuracy by enabling proper functioning of the pump check valves. The flow path continues to the permeate valve block, comprising four outlets, three of which allow for separation of the permeate from waste, concentration, and diafiltration operations. The fourth outlet is a preconfigured recycle line that is used for returning permeate back to the reservoir to allow steady state process analysis, such as during process optimization with TMP scouting.

Designed for process security

Pressure relief valves are incorporated into the retentate (R-VB-Out1) and permeate (R-VB-Out3) valve blocks as a security measure. Furthermore, the system and filter cartridges are protected against overpressure by pressure alarms in the UNICORN control software.

UNICORN software — a fast and secure way to work

UNICORN software offers full automation control of the ÄKTAcrossflow system. UNICORN has the benefit of one familiar control platform and user interface for all scales of operation in both filtration and chromatography. The scouting feature gives automatic support to process development and optimization. The ***Method Wizard***, which includes methods for sample processing as well as pre- and post-production filter preparation and cleaning, provides a high degree of efficiency in scale-up and production work. Also included with the UNICORN software are instructions that enable normal flow filtration operations. Data security and control enable compliance with 21 CFR part 11.

Filtration process control

The ÄKTAcrossflow system with UNICORN control software supports the process control modes commonly used in ultrafiltration and microfiltration applications, such as TMP control and permeate flow control. These control modes can be combined with selectable recirculation control, such as feed flow rate, feed pressure, delta pressure, retentate flow rate, or shear rate. The UNICORN software also reports real-time process data such as retentate volume, concentration factor, diafiltration exchange factor, and accumulated permeate volume.

Method creation

With the ***Method Wizard***, you can easily program your filtration method with all the steps in a typical run. For example, within one method, it is possible to rinse new filters and perform a normalized water permeability (NWP) test to check filter quality and status, before product steps of concentration and diafiltration, followed by a filter CIP, water flush, and a repeat of the NWP test. The NWP testing capability is a typical example of the benefits when using an automated system. Data from NWP tests for a certain filter can be gathered to check the flux recovery over multiple cycles.

For product steps, up to three concentration or diafiltration/wash steps can be selected (Fig 5). It is also possible to run in fed-batch or tank-batch mode, depending on your total initial processing volume.

A special option is the process optimization method, where you can scout recirculation rate and TMP values to find the optimal cross flow and TMP for your run. The method is linked to the evaluation module, where you can easily analyze your results.

A system sanitization method is also provided in the wizard.

Evaluation module

The ***Evaluation*** module saves you time by eliminating manual transfer of data to spreadsheets. The module allows flexible and direct presentation of optimization results with different evaluation operations including process optimization, NWP, diafiltration time optimization, capacity plots, and "any vs any".

Process optimization is used to analyze process characterization experiments where a series of set points are tested (Fig 6). The most common experiments are excursions of TMP at different cross flow rates and protein concentrations. Process optimization makes a new plot from user-identified points along original data curves, such as flux vs TMP (Fig 7). Process optimization also allows the user to overlay multiple plots (i.e., flux vs TMP at different cross flow rates or protein concentrations). This capability can be used for any process parameter.

The "any vs any" evaluation operation is used to analyze results from routine concentration, diafiltration, and cell processing runs. The "any vs any" evaluation allows you to plot any process parameter captured as a curve in any result file on either the x-axis or the y-axis.

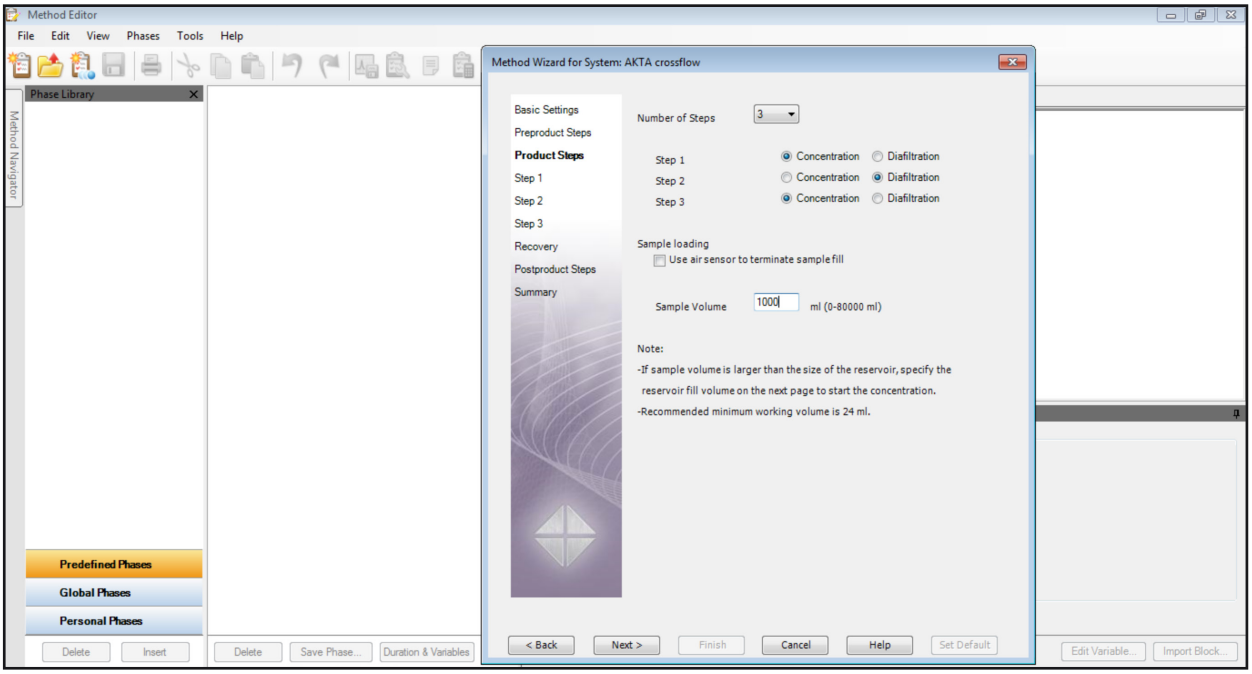

Fig 5. Product step selection in the ***Method Wizard***.

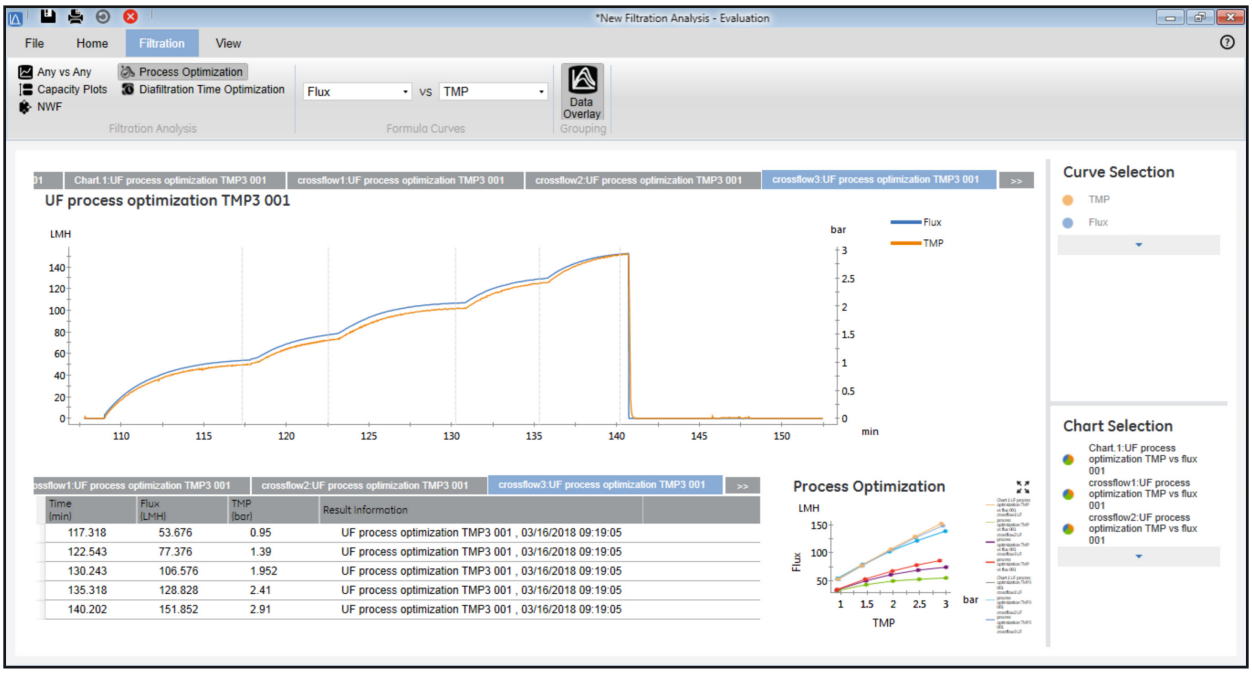

Fig 6. Raw data recorded from process optimization for BSA concentration/diafiltration using TMP scouting with 75g/L and 40g/L BSA solutions.

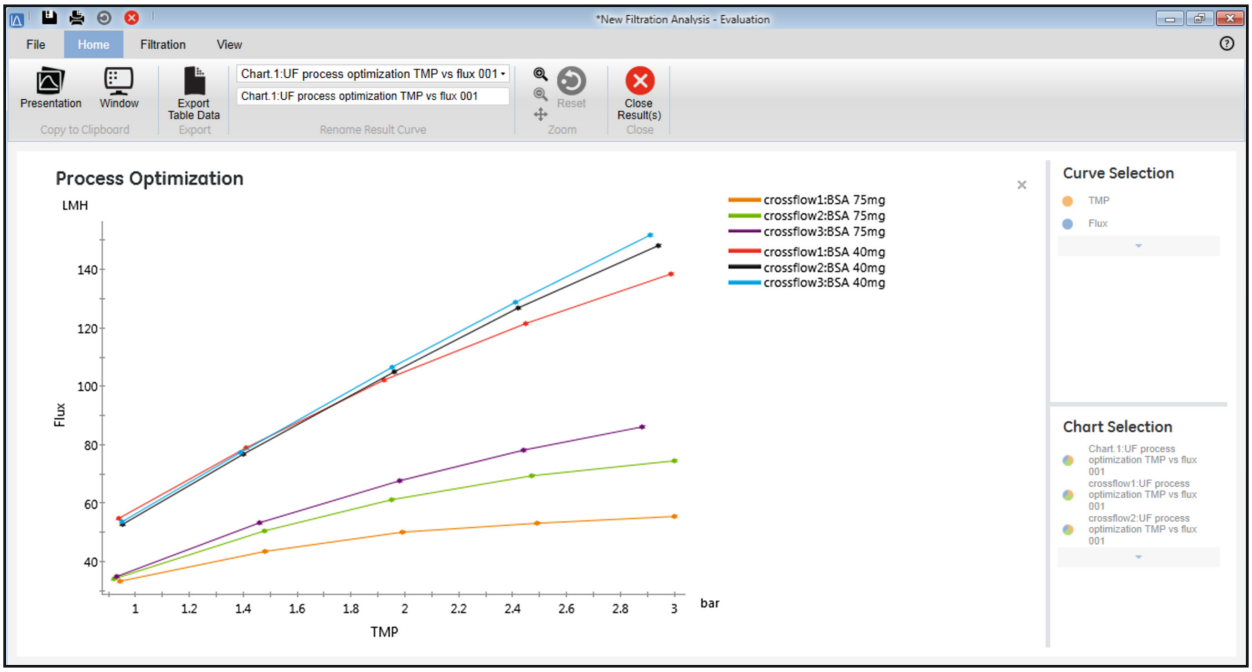

Fig 7. Curves generated in the ***Evaluation*** module from the raw data in Figure 8. The lower three curves show the results for 75g/L BSA, the upper three curves show the results for 40g/L BSA.

Filtration devices

The ÄKTAcrossflow system is suitable for use with a wide range of cross flow filtration devices, including Cytiva hollow fiber filter cartridges, for cell harvesting/concentration and product concentration/diafiltration. The system is designed to operate up to 1200 cm^2 of filter area for processing small sample volumes.

Design for easy sanitization

Sanitization is the use of a chemical agent to reduce a microbial population to an accepted, predetermined level. Microbial challenge tests evaluate the efficiency of the sanitizing agent.

The ÄKTAcrossflow system has a design that allows for effective sanitization using 1 M sodium hydroxide (NaOH) as a sanitizing agent. In a study, the system was challenged to a high level (1×10^6 colony forming units [CFU]/mL) of microbial contamination. A strain of bacteria recommended by the United States Pharmacopeia 27 (USP 27) for antimicrobial testing and a strain of yeast commonly used in the production environment were used as challenging organisms (Table 1). The results show that the suggested system sanitization method is sufficient for sanitization and that the numbers of viable organisms were sufficiently reduced.

Table 1. The organisms used in the microbial challenge tests

Escherichia coli	ATCC 8739	Gram negative bacteria
Pichea pastoris	GS155	Yeast

Validation documentation and services

Regulatory authorities expect companies producing therapeutic or diagnostic products to qualify equipment before use in production or analysis. The Fast Trak validation services team of specialists provides validation documentation on request after delivery of the ÄKTAcrossflow system. Installation and operational qualifications (IQ/OQ) of production and analysis equipment are part of the formal qualification required by cGMP. As such, this documentation is subject to inspection by regulatory authorities. Fast Trak IQ/OQ packages consist of professionally developed templates that will facilitate equipment qualification. The templates have help texts and are easy to complete or if assistance is required, Fast Trak validation services can complete the qualification for you.

Technical specifications

Technical specifications are listed in Table 2.

Table 2. Technical specifications for the ÄKTAcrossflow filtration system

Operating range	
Feed flow rate accuracy	1–600 mL/min, 2% within 2–600 mL/min
Transfer flow rate accuracy	0.1–200 mL/min, 0.5% within 2–200 mL/min
Permeate flow rate accuracy	0.1–200 mL/min, 0.5% within 2–200 mL/min
Max. system pressure	5.2 bar (75.4 psi)
Min. recirculation volume	< 25 mL (with 1.7 mm i.d. tubing)
Hold-up volume, recirculation line	< 20 mL (with 1.7 mm i.d. tubing kit, empty reservoir, excluding filter hold-up volume)
Reservoir max. hold-up volume	350 mL (375 mL without float) 1100 mL (1200 mL without float), (optional)
Recommended filter area	16–1200 cm^2
System specifications	
Dimensions (W × L × H)	620 × 400 × 650 mm
Weight, approximate	70 kg
Operating temperature	4°C to 40°C (50°C during membrane cleaning)
Detection and control	
Pressure transducers at cartridge (feed, retentate, and permeate) accuracy	0.01 bar (0.15 psi)
TMP control accuracy	0.05 bar (0.73 psi)
UV measurement	Hg lamp: 254 and 280 nm (other wavelengths optional; Zn lamp: 214 nm)
pH measurement	Range: 0–14 (spec. valid between 2 and 12)
Conductivity measurement	Range: 1 µS/cm to 250 mS/cm

Ordering information

Product	Product code
ÄKTAcrossflow	18118000
UNICORN 7 software license package for filtration and WAVE Bioreactor™ systems	29270760

Accessories

1100 mL reservoir	11003116

Hollow fiber cartridges

Model number	Pore size (NMWC)	Fiber i.d. (mm)	Membrane area (cm^2)	Nominal flow path length (cm)	Product code
Start AXM ultrafiltration cartridges					
UFP-3-C-2U	M_r 3000	0.5	50	30	11000543
UFP-10-C-2U	M_r 10 000	0.5	50	30	11000544
UFP-30-C-2U	M_r 30 000	0.5	50	30	11000545
UFP-100-C-2U	M_r 100 000	0.5	50	30	11000546
UFP-300-C-2U	M_r 200 000	0.5	50	30	11000547
UFP-500-C-2U	M_r 500 000	0.5	50	30	11000548
UFP-500-E-2U	M_r 500 000	1.0	50	30	11000549
UFP-750-E-2U	M_r 750 000	1.0	50	30	11000550
UFP-750-C-2U	M_r 750 000	0.5	50	30	29008269
Start AXM microfiltration cartridges					
CFP-1-E-2U	0.1 µm	1.0	50	30	11000551
CFP-2-E-2U	0.2 µm	1.0	50	30	11000552
CFP-4-E-2U	0.45 µm	1.0	50	30	11000553
CFP-6-D-2U	0.65 µm	0.75	50	30	11000554
Start AXH ultrafiltration cartridges					
UFP-3-C-H24U	M_r 3000	0.5	40	60	11000537
UFP-10-C-H24U	M_r 10 000	0.5	40	60	11000538
UFP-30-C-H24U	M_r 30 000	0.5	40	60	11000539
UFP-100-C-H24U	M_r 100 000	0.5	40	60	11000540
UFP-300-C-H24U	M_r 300 000	0.5	40	60	11000541
UFP-500-C-H24U	M_r 500 000	0.5	40	60	11000542
UFP-750-C-H24U	M_r 750 000	0.5	40	60	29008270
Start AXH microfiltration cartridges					
CFP-1-E-H22U	0.1 µm	1.0	40	60	56411028

Cell Processing Evaluation Kit

Model number	Description	
CFP-CELL-KIT-2U	Contains 1 each of UFP-750-E-2U, CFP-1-E-2U, CFP-2-E-2U, CFP-4-E-2U, CFP-6-D-2U	11000565

Related literature

UNICORN 7 system control software, Data file	29135786
Cross Flow Filtration Method Handbook	29085076

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