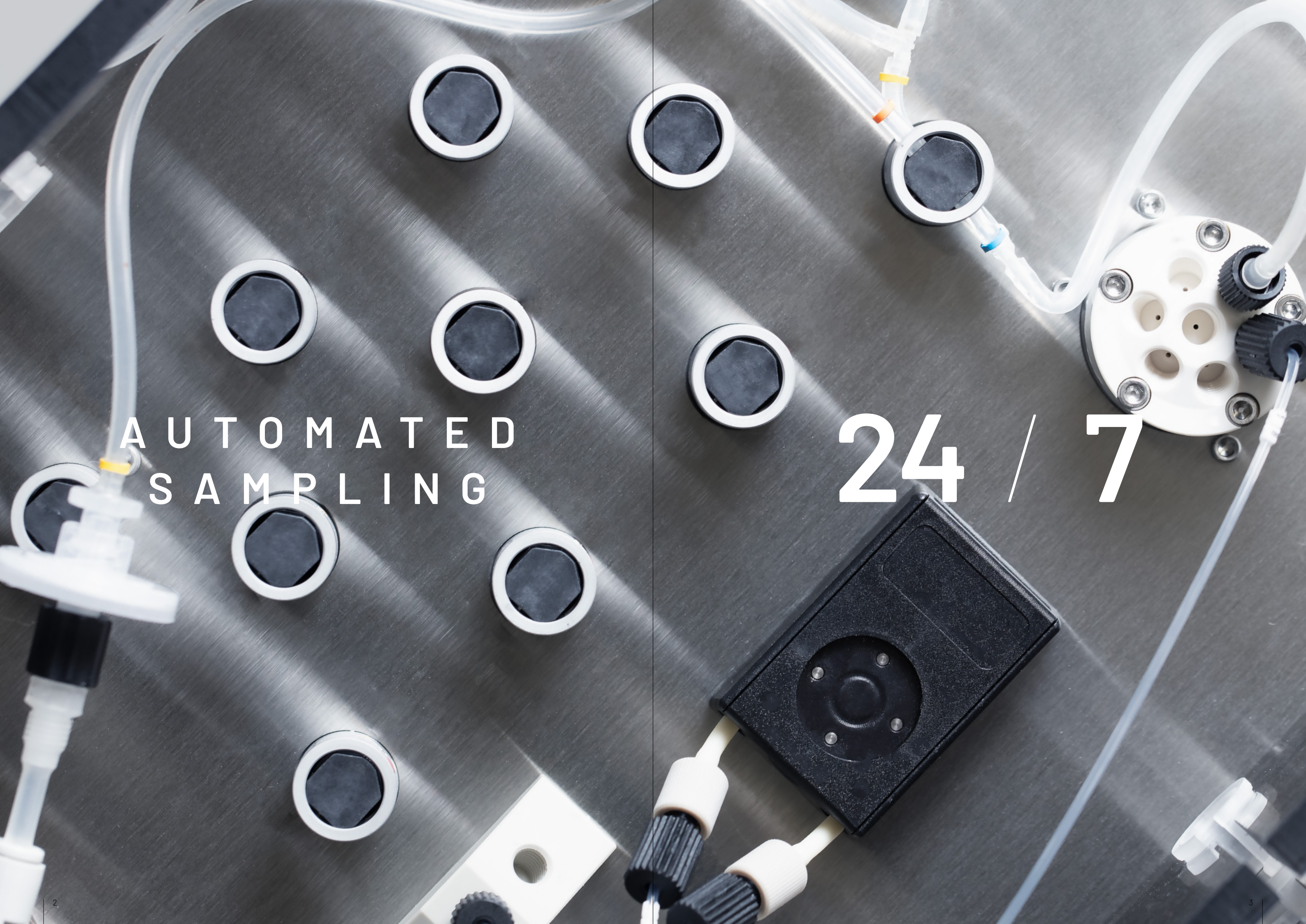




ADVANCED BIOPROCESS SAMPLING SOLUTION





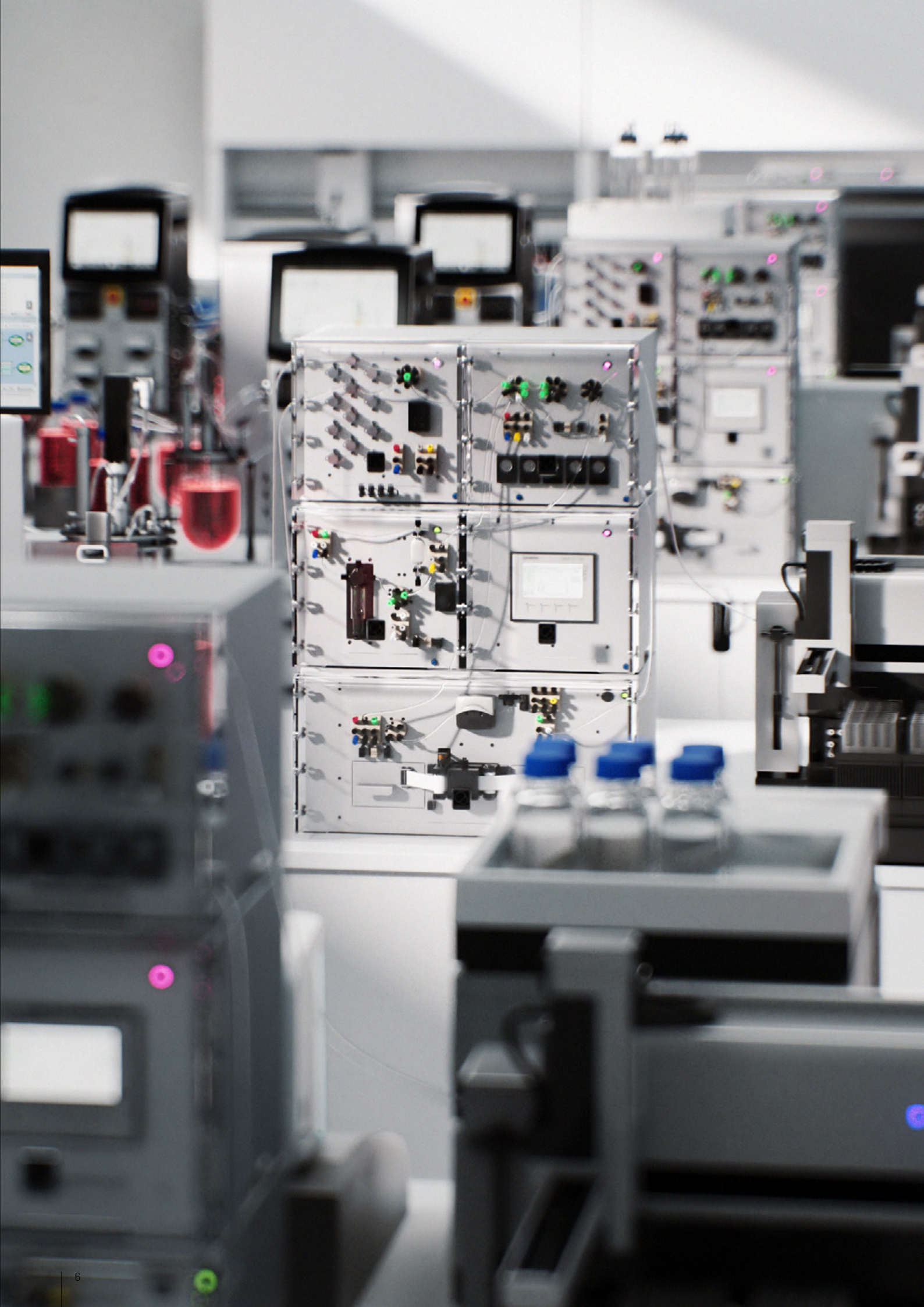
AUTOMATED
SAMPLING

24 / 7

Numera® is a fully automated sampling system that never sleeps, integrating and improving every process analytical technology with reliable real-time results 24/7.

CONTENT

Main Devices	8
Product Configuration	12
Reactor Connection	14
Sampling & Sterility Concept	17
Analyzer Integration	20
Sample Management	23
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MAIN BENEFITS

- Automated sampling 24/7
- High frequency and low volume
- Individual sample preparation including dilution and consistent cell removal
- On-line measurements with common analyzers
- Automated data import from analyzers and advanced feedback control loops in combination with Lucillus®

KEY FEATURES

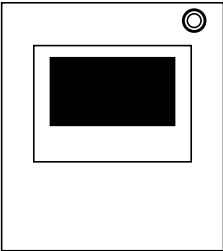
- Sampling from up to 16 vessels
- Sampling volume of 2 – 10 ml
- Sampling time of 8 – 17 minutes
- Sample storage and cooling (4 – 20°C)
- Sample transfer to 4 analyzers
- Unique filtration technology for cell removal

MAIN DEVICES

Numeras[®] is a modular PAT system. Each installation includes a Control Module, a Routing Module and at least one Multiplexer Module. The Dilution and Filtration Module for sample preparation are optional accessories.

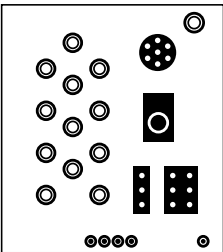
Control Module

- Touch screen
- Configurations settings for system preparation, cleaning, and settings
- Various communication ports
- Compressed air distribution



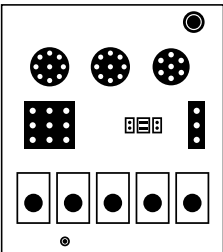
Multiplexer Module

- Multiplexing of up to 4 bioreactors per module
- Up to 4 modules per Numeras[®] system
- Pinch valve sterility barrier with ethanol rinsing
- Sterile air blow-back mechanism to prevent cross-contamination and preserve low volume sampling



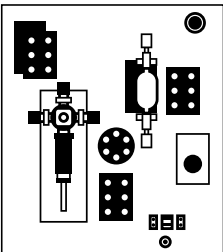
Routing Module

- Individual sample distribution within one process
- Transfer to 4 analyzers (biochemical analyzers or cell counter)



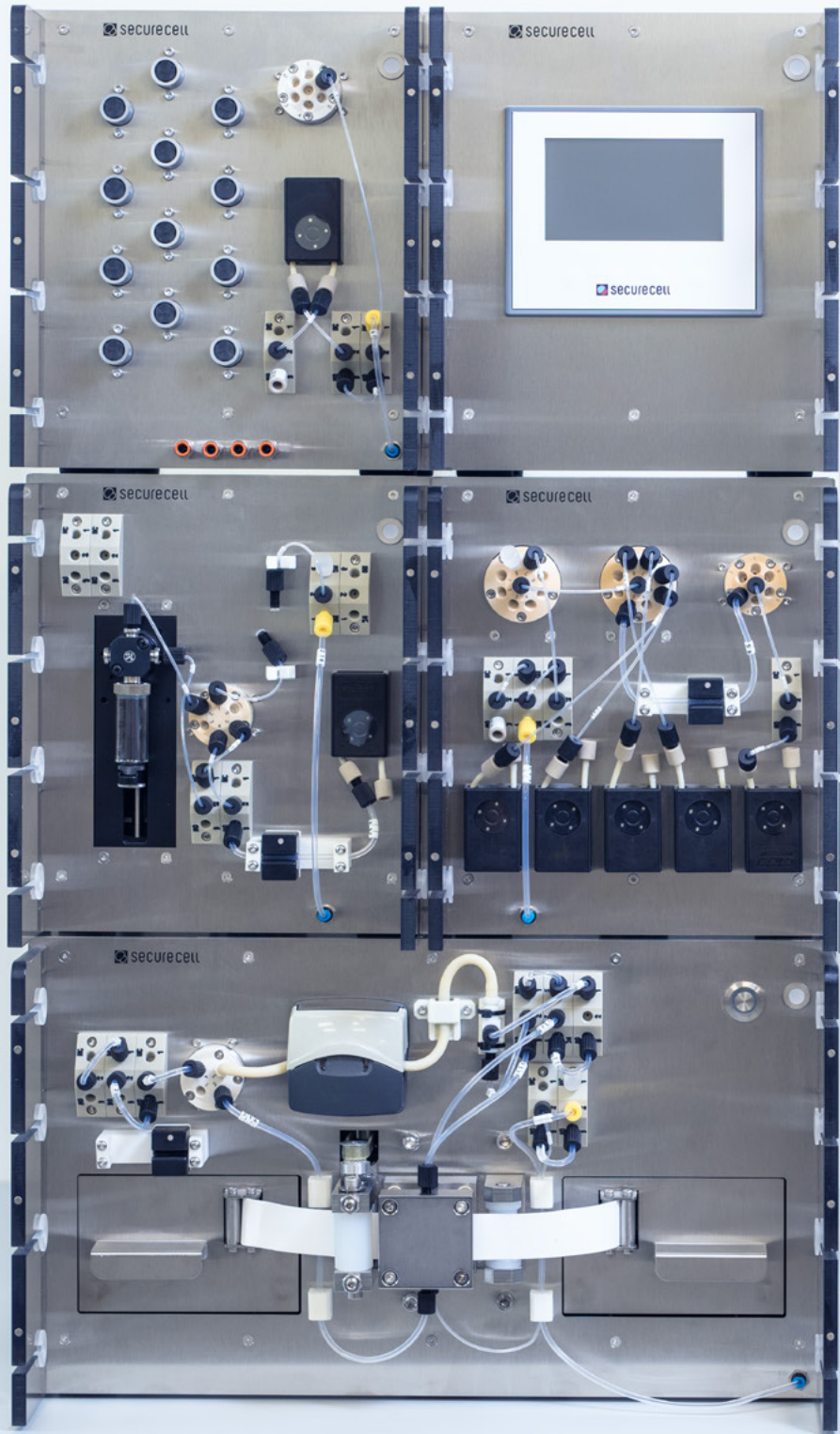
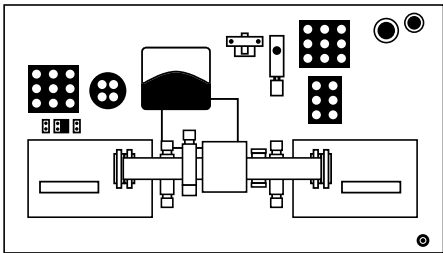
Dilution Module

- Dilution from 1:2 to 1:30
- Reagent addition, mixing, and incubation
- Precise and reproducible sample processing



Filtration Module

- Unique cross-flow filtration technology
- Low protein binding PES membrane coil
- 700 filtrations per coil
- Membrane pore sizes: 0.22 μm , 0.45 μm , and 1.2 μm
- Fresh membrane section for every filtration cycle avoiding cross-contamination





The Autosampler is equipped with Peltier cooling racks and can be used with various sample vials from 1.5 to 10ml. The device is available in two sizes with space for up to 384 vials.

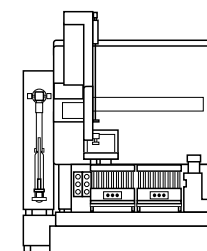
AUTOSAMPLER / SAMPLE COLLECTOR

Storage of retain samples or intermediate storage of samples for further processing is performed with the Autosampler. In addition, manually taken samples can be stored for processing with the Numera® and/or for transfer to analyzers. Cooling is guaranteed in a range of 4 to 20 °C. There are two different sizes of Autosampler available. Both are equipped with a syringe pump and a rinse station.

The Autosampler can be equipped with 2 well plates per Peltier rack module. Securecell offers well plates for 1.5 ml and 4.0 ml glass vials. Standard deep-well plates with 2, 5 or 10 ml can also be used.

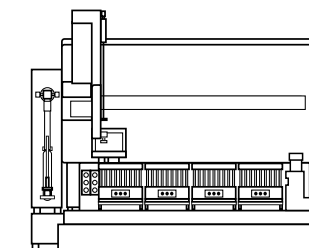
ASX-7200

- 2 Peltier rack modules (storage at 4 to 20°C)
- 4 well plate positions
- Optional: 1 HPLC injection valve



ASX-7400

- 4 Peltier rack modules (storage at 4 to 20°C)
- 8 well plate positions
- Optional: 1 or 2 HPLC injection valve(s)



ACCESSORIES

Well plates

- 40 × 1.5 ml vials
- 24 × 4.0 ml vials
- Standard deep-well plates with 2, 5, or 10 ml

HPLC/UHPLC injection valves

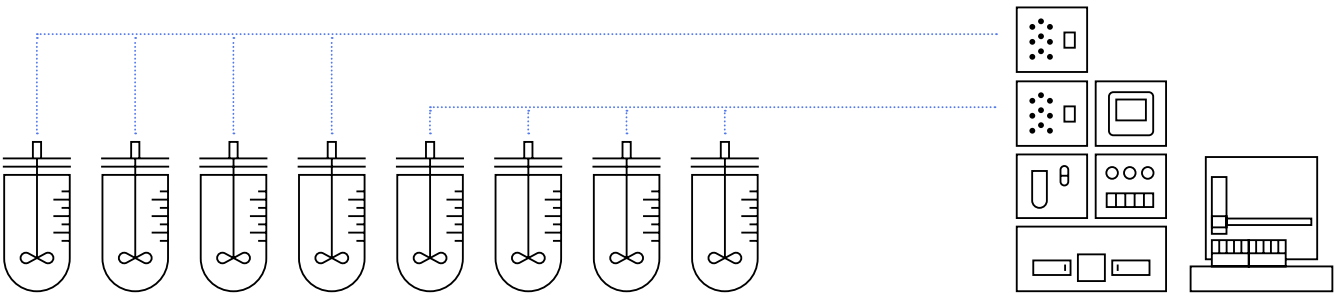
- Variants of 5.000 and 20.000 psi
- Vertical port injector
- Sample loop (ID 0.14 mm) from 5 to 50 µl

FLEXIBLE PRODUCT CONFIGURATION

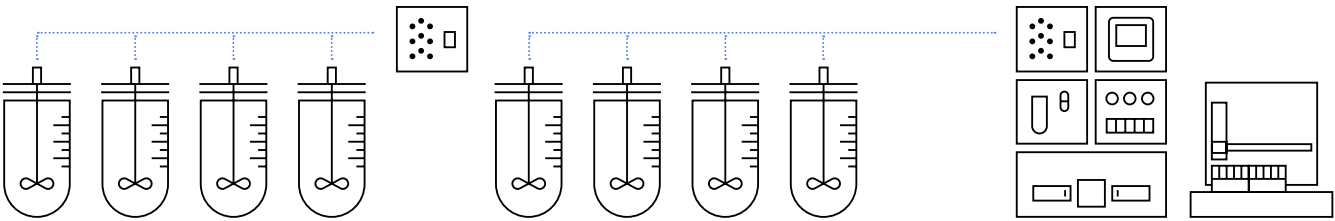
The modular design of Numera® allows configurations for single reactor sampling and storage up to multiple reactor sampling including dilution, filtration and integration of various on-line analyzers.



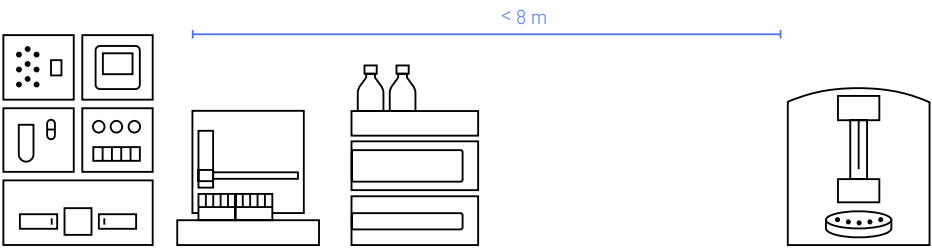
A maximum length of 10 m between the Numera® and the reactors is recommended.



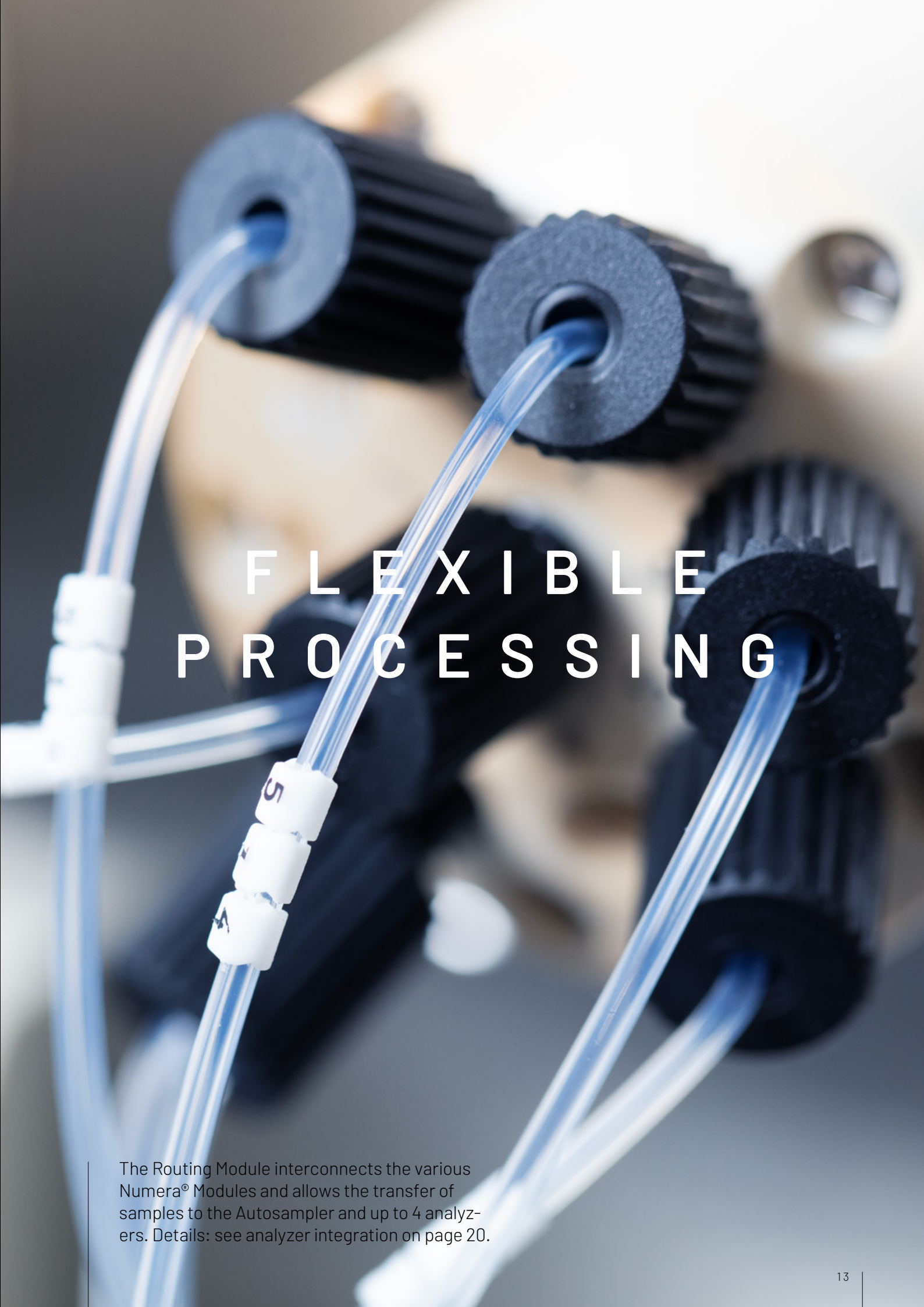
Up to 4 Multiplexer Modules can be stacked on a central system. This allows to connect up to 16 bioreactors.



Multiplexer Modules can be decentralized, depending on the available space and laboratory organization.



The Autosampler should be put close to the system. The distance to connected analyzers is limited to 10 m.



FLEXIBLE PROCESSING

The Routing Module interconnects the various Numera® Modules and allows the transfer of samples to the Autosampler and up to 4 analyzers. Details: see analyzer integration on page 20.

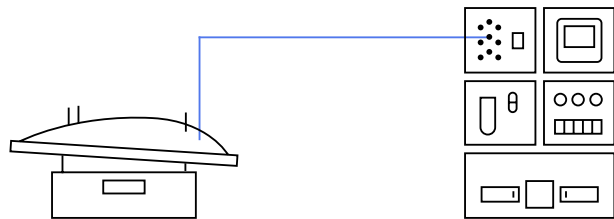
REACTOR CONNECTION

Numeras can be used in many applications – from single use, bench-top reactors, up to production. The appropriate connection options are available for all purposes. The modular concept includes:

- Single-use sampling sets
- Sample lines 1 – 10m

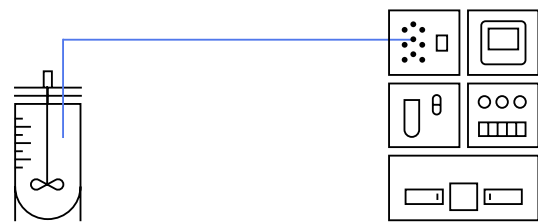
Single Use Bioreactors

- + Sample lines



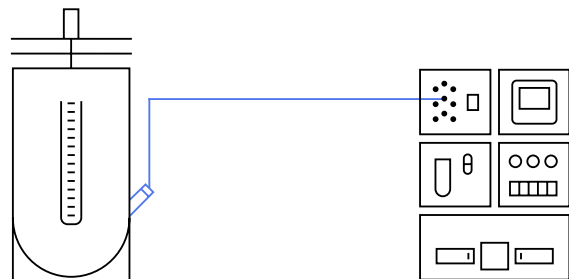
Benchtop Reactors

- + Sample lines
- + Dip tube
- + Adapters



Stainless Steel Reactors

- + Sample lines
- + Sampling port



At the Multiplexer Module, autoclavable **single-use sampling sets** including all tubings for sterile sampling, ethanol cleaning and blow-back with sterile air, are installed for each sample vessel.



Sample lines from 1 to 10 meters are used to attach the sampling set at the Multiplexer Module to the corresponding bioreactor interface with Luer-Lock screw connections.



Stainless steel **dip tubes** with a Luer-Lock connector are used in combination with a suitable reactor adapter to sample from bench-top (glass) bioreactors.



Adapters from 10 – 19 mm and PG13.5 are available to mount the dip tubes to any common head-plate port.



The **aseptic sampling port** enables sampling from stainless steel bioreactors using the 25 mm side port. The connection to the Numeras System is made with a septum piercing needle with side entry. The needle comes with a holder that fits to the aseptic sampling port and with a Luer-Lock connector.



STERILE INTERFACE

The Multiplexer offers 4 connections for single use sampling lines, to interface bioreactors or downstream vessels. Sterility is ensured through pinch valves and ethanol. A Numera® system can include up to 4 Multiplexer Modules.

SAMPLING & STERILITY CONCEPT

- Minimal sample loss
- No sample dilution
- Guaranteed sterility
- No cross contamination

Sample lines and sampling sets are auto-claved in bags before use and protected with sterile air filters and clamps to maintain sterility during installation.

The clamps are removed after mounting the tubes on the pinch valves. The tubes are subsequently connected to the Multiplexer Module input and to the bioreactor/vessel interface. Luer-Lock screws ensure the connection between sampling set, sample line and bioreactor interface.

After completion of the sampling procedure, the remaining sample in the sampling line is pushed back into the bioreactor with sterile air. An ethanol rinsing procedure cleans the sampling sets at the Multiplexer Module to remove sample residues and prevent contamination. A water rinsing procedure guarantees complete removal of ethanol.

Proof of sterility in a technical run

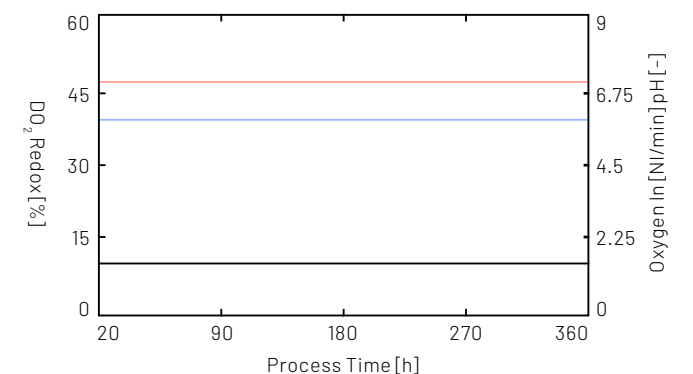


Figure values for pH (red line), pO₂ (blue line) and O₂ inflow (black line) over process time. The steady values indicate a sterile process over 15 days. Samples were drawn every 2 h.

Full article on our [website](#).



U N I Q U E

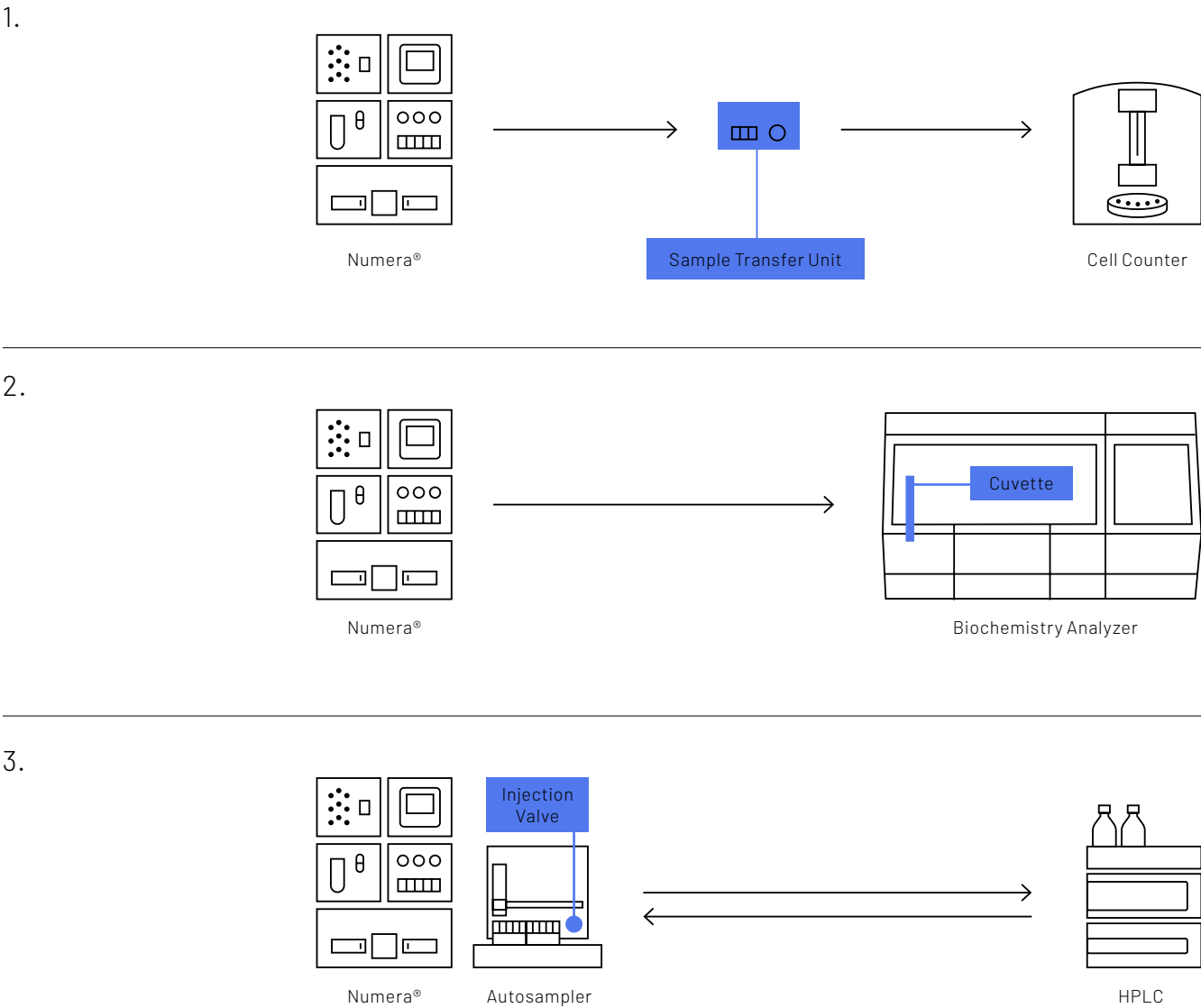
F I L T R A T I O N

The unique cross-flow tape filtration technology enables gentle and complete cell removal with low sample volumes. Various pore sizes from 0.2 to 1.2 μm are available.

Numerar[®] can be used in combination with various analyzers to perform on-line analytics:

- 1. Cell counters (e.g., ViCELL XR[®], Cedex HiRes)
- 2. Biochemistry Analyzers (e.g., Cedex[®] Bio HT)
- 3. HPLC Sytems (e.g., Agilent 1100/1200 Series, Thermo Fisher Vanquish)

For each analyzer integration, specific accessories and information are needed that are provided by Securecell.



HPLC INTEGRATION

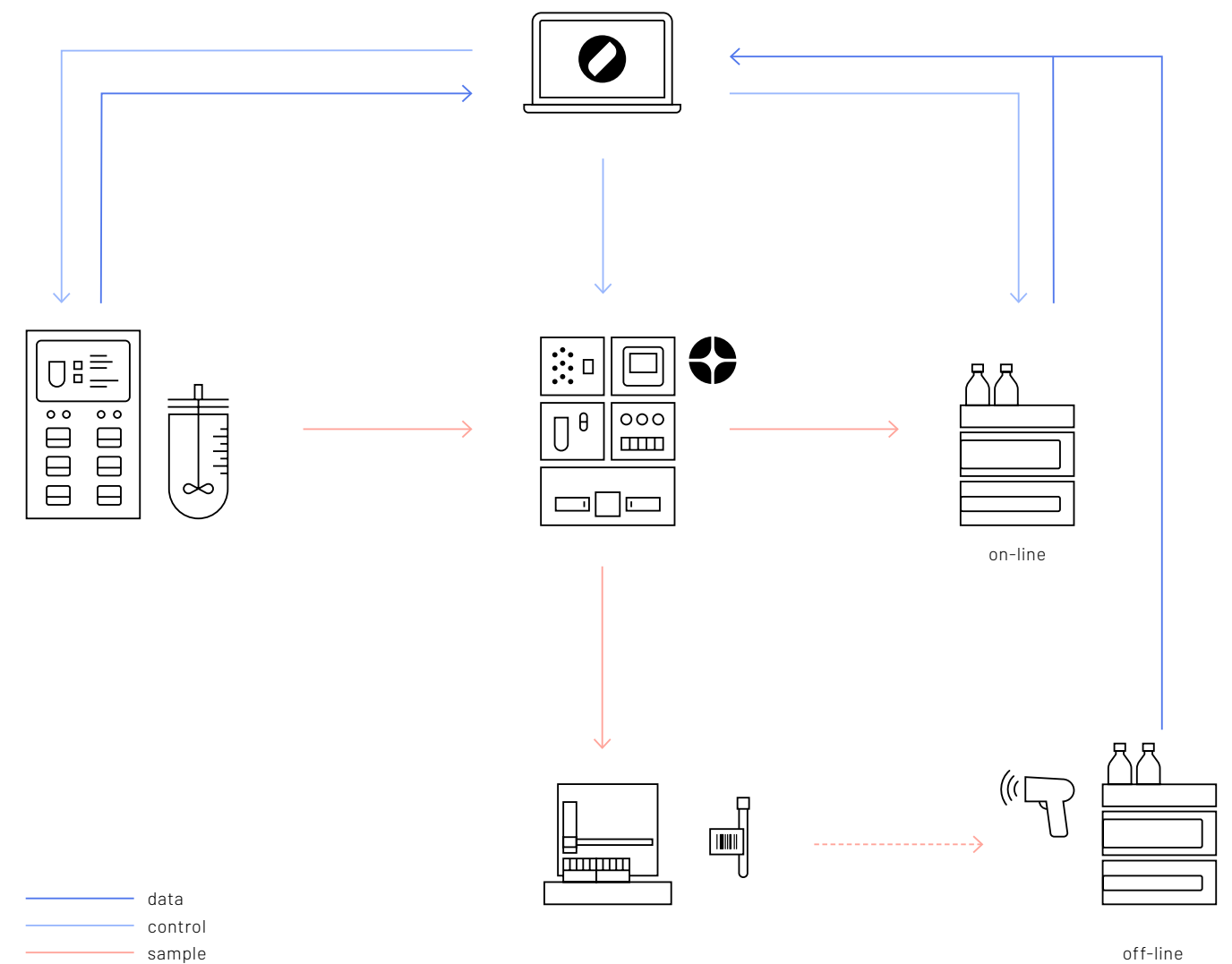
An injection valve for HPLC (up to 20'000 psi) can be included in the Autosampler setup. Direct inject provides loss free and fast analytics with HPLC system of various vendors.



SAMPLE MANAGEMENT

The combination of the automated sampling system, Numera®, and the Process Information Management System, Lucullus®, enables the orchestration of the whole workflow covering sampling, measurement, process monitoring and control.

- Sample planning (time and event based)
- Analytical methods for all analyzers
- Barcode and label printing
- Automated event-based sample triggering during process
- Sample preparation and sample storage
- Automated on-line measurements
- Centralized data management and process monitoring
- Advanced process control and feedback loops



"High-density, time-resolved data reduce the number of experiments."

PROF. CHRISTOPH HERWIG
Professor for Biochemical Engineering, TU Wien

APPLICATION EXAMPLE

On-line HPLC analysis and data integration with Numera® and Lucillus® PIMS shown on the example of a CHO process

Alexandra Hofer and Paul Kroll, Securecell AG
Christoph Herwig, TU Wien

In this application note monitoring of a CHO process by automated sampling and sample processing with the Numera® system and an on-line Thermo Scientific™ UltiMate™ 3000 HPLC system is demonstrated. High-frequency data of product and B-vitamins is shown, illustrating the benefits of automated sampling. Additionally, data integrity can be guaranteed by the Process Information Management System Lucillus®, merging all data attached to a process including results of the on-line analytics.

Full article on our [website](#).

Figure 1: Comparison of the concentrations of manual samples measured off-line and automatically drawn samples measured on-line. Both analyses are in perfect accordance, if minor sample dilution via the system is considered. Compensation of the sample dilution can be performed by processing the standards for calibration with Numera® resulting in an offset of 0.03% (light blue upside-down triangles) or by calculation of the dilution factor resulting in an offset of 0.01% (red triangles) analysis.

- calib [slope = 0.97]
- calc [slope = 0.99]

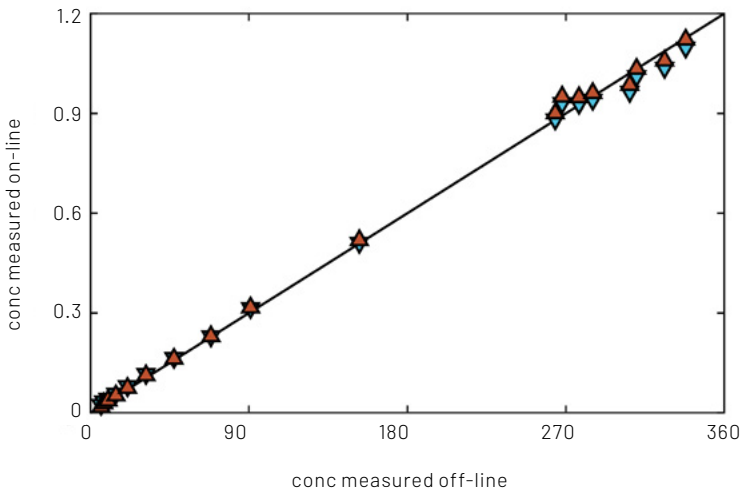
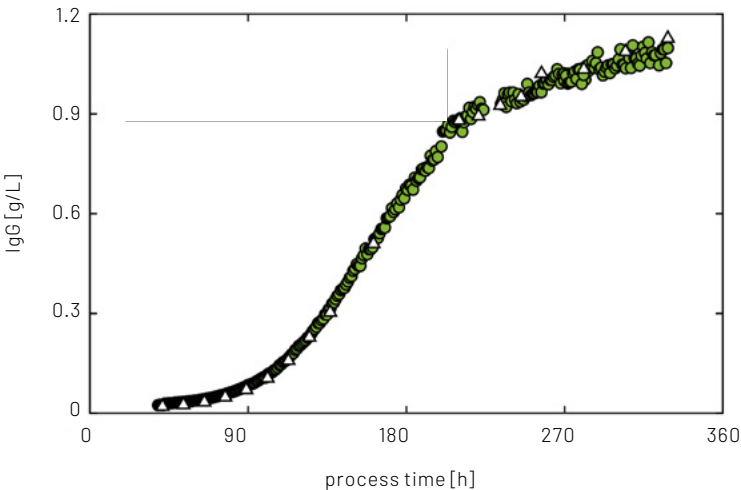


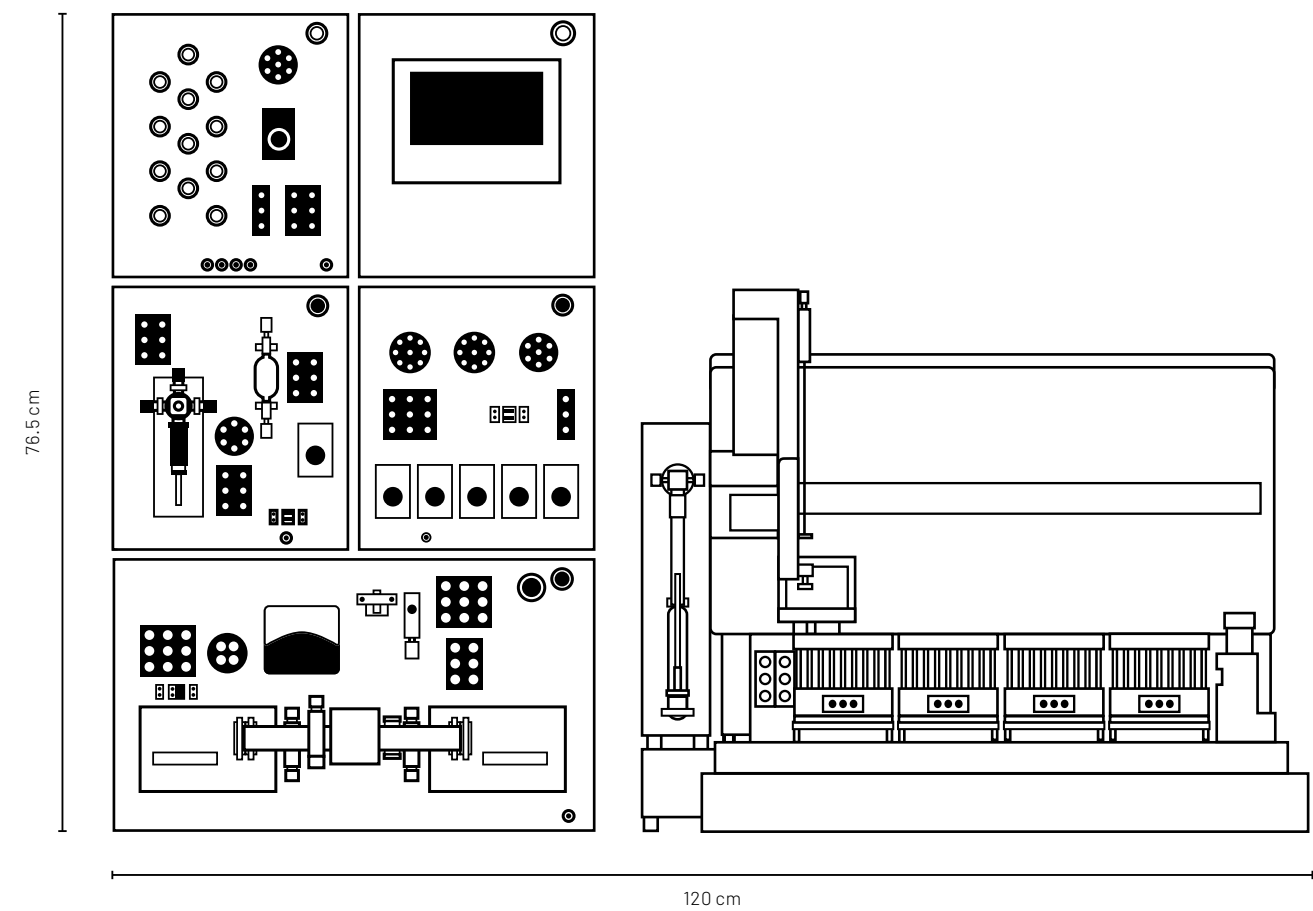
Figure 2: The production of IgG over process time can be seen with the on-line as well as the off-line data. The results are in good accordance. Between 160 h and 210 h the process was unattended; hence, just automated samples were drawn.

- on-line sample
- off-line sample



TECHNICAL DATA

Dimensons and Weight



Numera® Modules

	Dimension (w × h × d)	Weight
Control Module	22 × 22.5 × 30 cm	8.5 kg
Multiplexer Module	22 × 22.5 × 30 cm	8.6 kg
Dilution Module	22 × 22.5 × 30 cm	9.4 kg
Routing Module	22 × 22.5 × 30 cm	11.0 kg
Filtration Module	44 × 25.5 × 30 cm	21.5 kg

Autosampler

ASX-7200	37 × 46 × 54 cm	21.0 kg ¹
ASX-7400	57 × 46 × 54 cm	23.0 kg ¹

SPECIFICATIONS

Sampling frequencies

The sampling frequencies depend on the applied sample processing and the length of the sampling lines.

Sample Processing ²	Duration (mm:ss) Processing ³	Cleaning	Total	Frequency	
Direct transfer	02:50	06:40	09:30	6.3 h ⁻¹	~150 day ⁻¹
Sampling + Filtration	01:45	06:45	08:30	7.0 h ⁻¹	~170 day ⁻¹
Sampling + Dilution	06:00	11:00	17:00	3.5 h ⁻¹	~85 day ⁻¹
Sampling + Dilution + Filtration	05:20	06:50	12:10	5.0 h ⁻¹	~120 day ⁻¹

Sampling volume

Approximate values for sample volume, rinsing solution and cleaning solution (ml).

Sample Processing ²	Sample Volume	Sample Used	Total Volume	Cleaning Solution	Rinsing Solution
Direct transfer	1.4	1.2	2.7	2.0	4.2
Sampling + Filtration	1.4	2.3	3.7	11.9	38.7
Sampling + Dilution (1:2)	1.6	1.9	3.6	12.0	18.0
Sampling + Dilution (1:20)	1.7	0.6	2.3	11.9	18.1
Sampling + Dilution + Filtration (1:2)	1.4	2.3	3.7	21.6	38.7
Sampling + Dilution + Filtration (1:20)	1.5	0.9	2.3	21.2	38.4

- 1. Without syringe module, Peltier racks, and injection valve.
- 2. All experiments were performed with water at room temperature. Reactor connection tube length: 1.5 m (ID 0.75 mm). No overpressure in the reactor, 155 rpm pump in SRU and SDU. Dilution ratio 1:2 and 1:20.
- 3. Including sampling and transfer to Autosampler.



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