TOSOH

Octave™ Multi-Column Chromatography

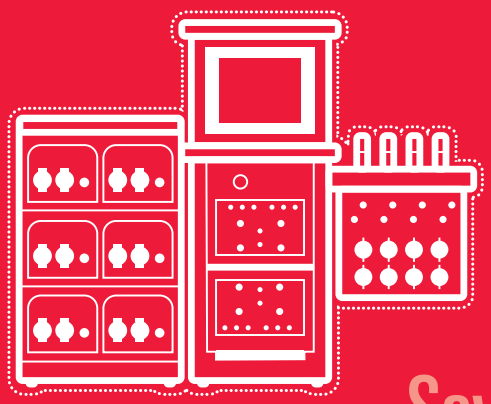
A holistic solution for process intensification

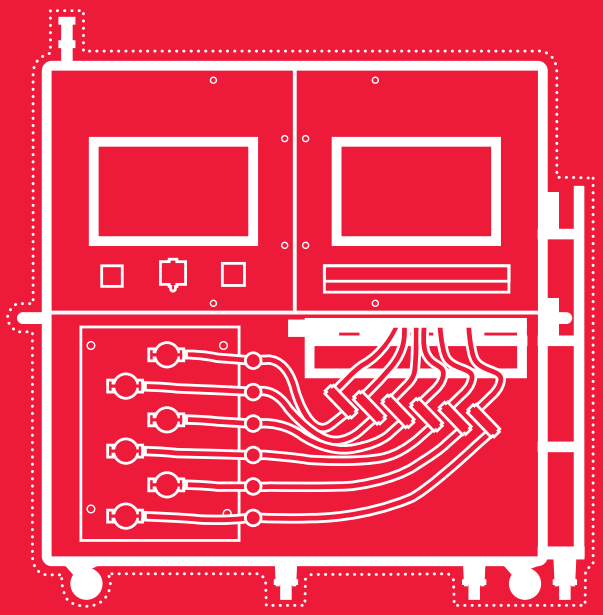
Method Development

Octave PRO

Production

Octave BIO





MCC

Reduce Operating Costs

Save Time

Increase Productivity

Scalability

SkillPak

Bioprocessing

Flexibility

Experts in Chromatography

TOSOH BIOSCIENCE

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Process intensification – The paradigm shift in process chromatography

Despite advances in the processing and manufacturing of biological therapeutics, downstream purification (DSP) of molecules is still a time, resource, and cost intensive procedure. Furthermore, advancements in upstream production have served to exacerbate bottlenecks of current DSP processes.

The default approach to DSP is to sequentially process liquids batchwise via disjointed unit operations (e.g. filter and liquid chromatography systems). Chromatography steps often contribute most to time, resource, and cost inefficiencies, where large columns and large volumes of expensive affinity resin are operated at long residence times and used to purify comparably small volumes of product. This lack of productivity can be overcome using novel approaches, namely multi-column chromatography (MCC), which offers the following benefits over batch chromatography.

While the adjacent small molecule pharmaceutical industry already benefits from introducing continuous chromatography (e.g. for xylol or enantiomer production) the biologics industry is just now adapting the MCC technique for intensifying purification. Seeking highly efficient purification to address resource and throughput concerns, industry leaders and visionaries are already adapting MCC to accommodate fast growing and agile biopharma market trends. This is strongly supported by regulatory bodies like the FDA, who identified a need to transfer daily workflow towards continuous downstream processing (Guideline ICH Q13).

Transition to MCC

Batch Processing

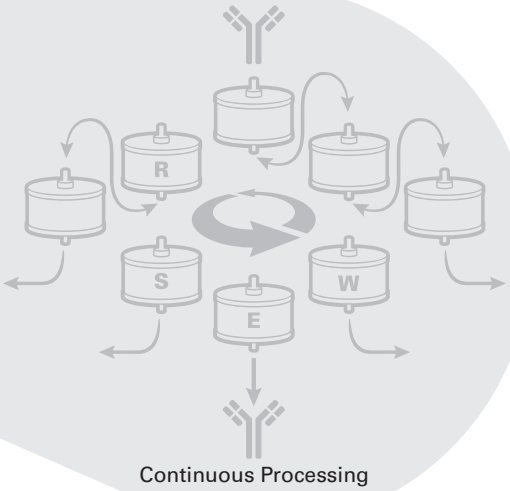
Up to 90% resin savings
due to higher productivity

Up to 40% solvent savings
due to better utilization of the column bed

Up to 5 x smaller footprint
due to smaller buffer vessels, columns, and instrumentation

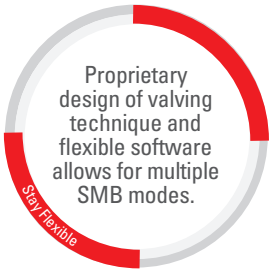
Seamless volume scale-up
(mg- to kg-range of purified product)
due to overall effectiveness, continuous loading technique, and availability of columns

End-of-lifetime usage of resin batch
due to continuous nature of the process



Continuous Processing

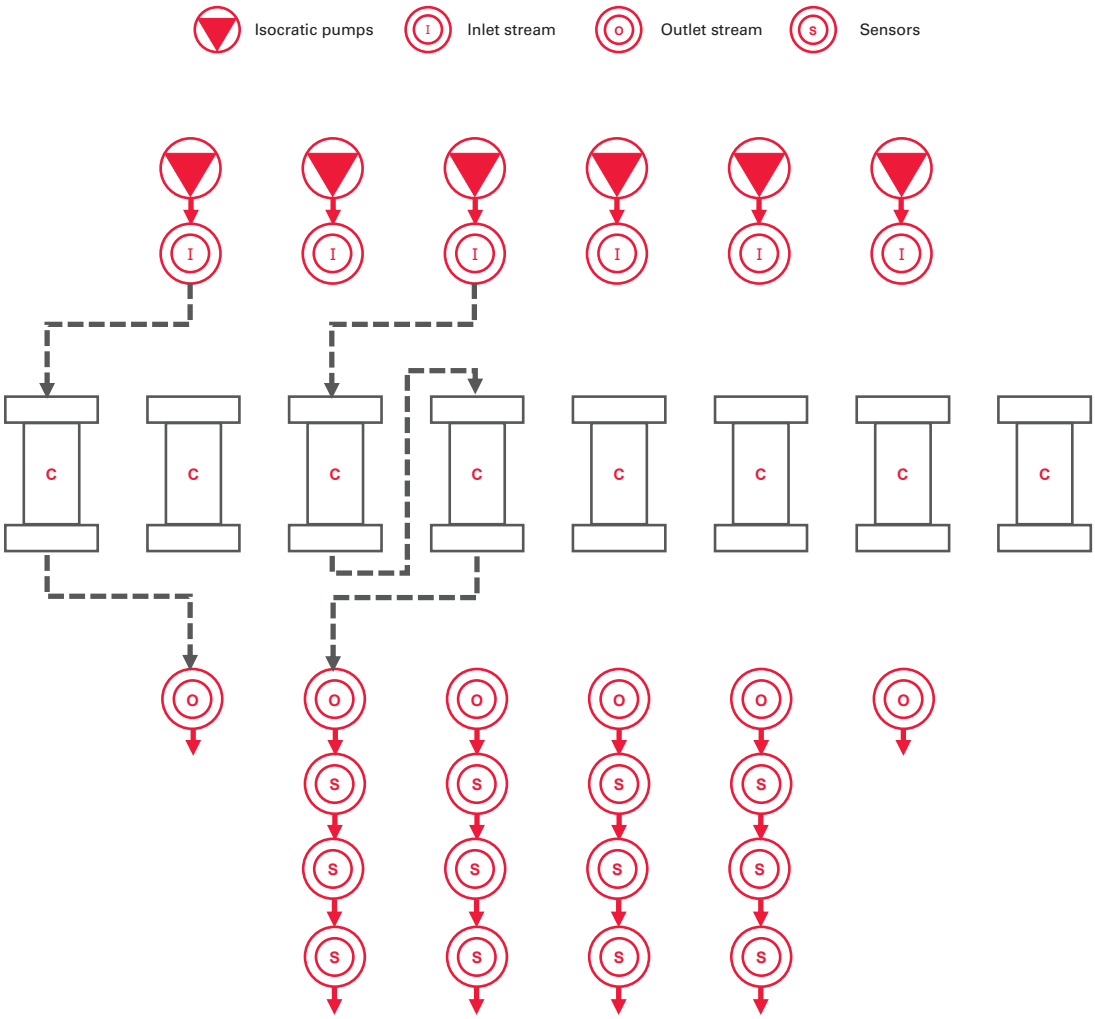
Working principle of MCC in bioprocess



Multi-column chromatography is a bioprocessing technique which uses a set of small process columns to continuously load and process a product stream and generate purified product with comparable yield and product quality under high-throughput conditions. Typically, these MCC columns have a shorter bed height, and enable processing at faster flow rates to achieve greater efficiencies. To better utilize the capacity of each column, especially at these faster flow rates, two to three interconnected columns are typically loaded simultaneously.

Our MCC instruments are comprised of a set of isocratic pumps, a valve manifold with six inlet and six outlet streams, (the columns, and a set of sensors that work in conjunction to both operate and monitor all of the process columns simultaneously. All our systems are based on this architecture to make processes scalable. At any given time, each column is undergoing a different process step, and the valve block technology of our systems simplifies these simultaneous sets of operations.

Moreover, this can be changed during the run – by doing so the columns can be attributed to different solvent streams in a cyclic manner – the famous moving bed.

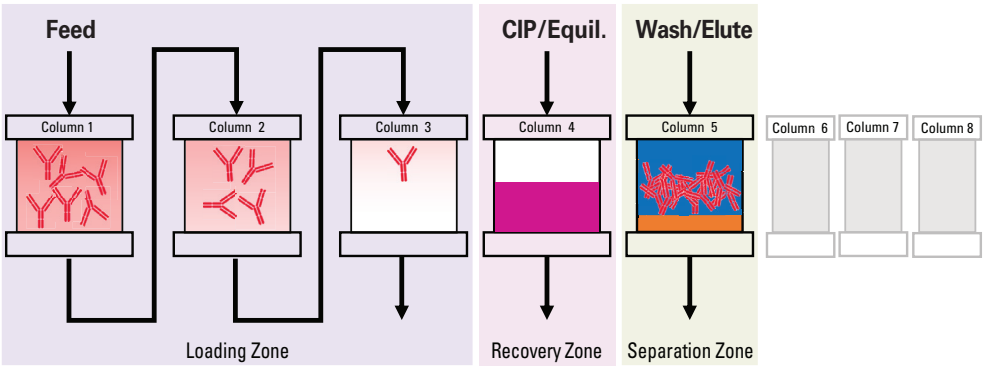


Purification of biomolecules via capture chromatography

Typical implementations of MCC in bioprocessing are for affinity steps with a bind and elute mode of operation (step mode) to purify antibodies, recombinant proteins, or peptides.

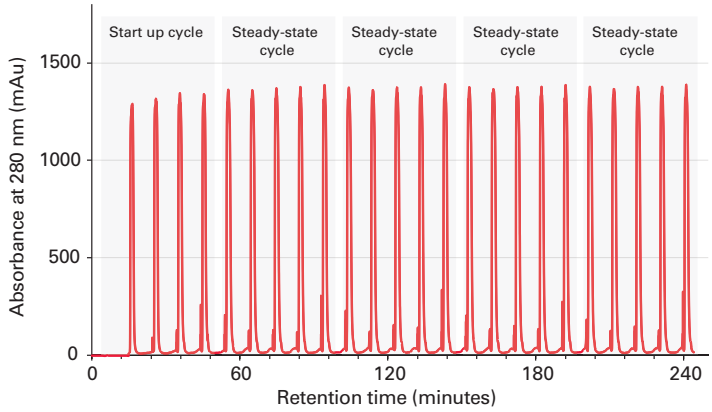
The five steps of affinity chromatography (feed, wash, elute, clean, and equilibrate) are conducted with the column set as follows: Every moment three columns are being loaded (loading zone), whereas all residual steps are conducted simultaneously on the remaining columns (Separation and Recovery Zone).

Depending on the experimental variables (capacity, max. flow rate, number of washing steps, titer etc.) the number of columns utilized for your process may vary. That's why our instruments utilize up to 8 columns.



During a run, the sensor sets generate a user defined live view of the process monitoring the outlet streams of zones of interest. In the separation zone, each peaks monitored during the elution step indicates the elution of bound biomolecules from one column.

The chromatogram shown exemplarily illustrates the purification of mAbs from a clarified cell culture supernatant. Direct comparison of process performance using a column with equal total resign volume operated in batch mode reveals productivity gain of ~ 300% for the transition to MCC underlining the potential of continuous biochromatography for time and costs savings.



Column set: 5× SkillPak™ BIO AF-rProtein A HC-650F, 0.8 cm ID × 2 cm length each
Sample load: 85% of static binding capacity, 463 mL feed stock solution processed in total
Process liquids: Feed (3.4 g Adalimumab/L from clarified Chinese hamster ovary cell culture supernatant), Wash (100 mmol/L NaP pH 7.0), Elution (100 mmol/L NaAc pH 3.0), CIP (200 mmol/L NaOH), Equilibration (100 mmol/L NaP pH 7.0)

Mode	Column volume (mL)	Cycle time (min)	Residence time (min)	Recovery (%)	Utilized capacity (mg prod/mL resin)	Buffer consumption (mL buffer/mg prod)	Productivity (mg Prod/(mL resin*h)
Batch	1 × 5	160	5.00	97.9	48	0.64	17.5
MCC	5 × 1	49	0.50	97.1	63	0.44	71.1

300%

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Process Development

No compromises! Octave BIO offers these modes:

- Step mode
- Isocratic mode
- Batch mode
- Gradient mode
- Parallel LC mode

Want to learn more? Visit our website.

Octave BIO

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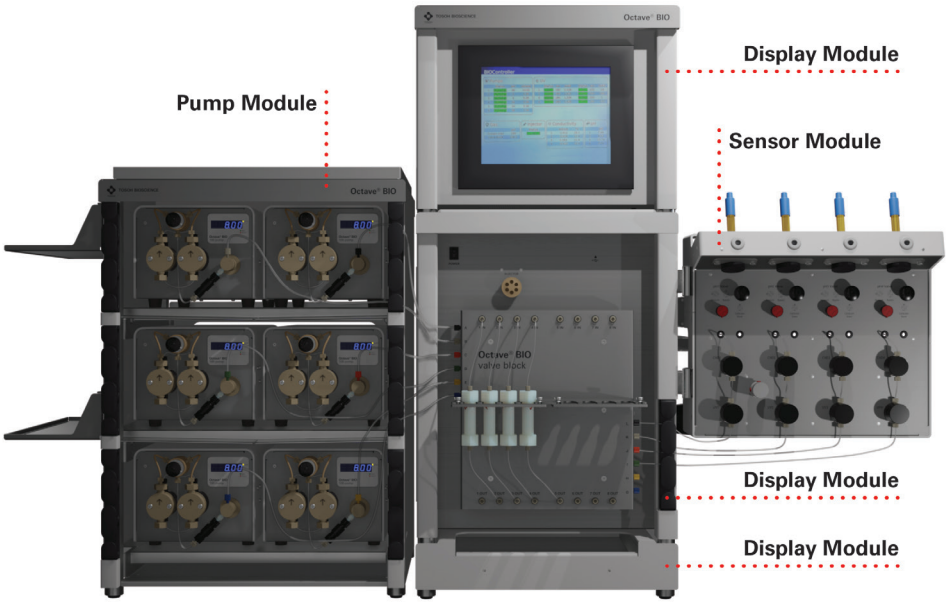


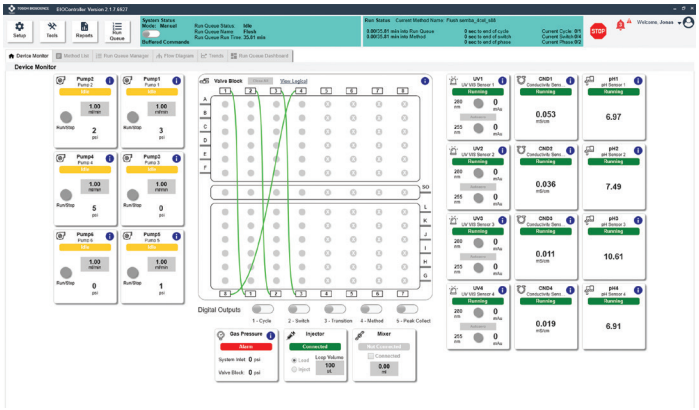
The Octave BIO from Tosoh Bioscience is the most comprehensive and versatile multi-column chromatography (MCC) system for process development and proof of concept. The unique modular and bio-compatible design is tailored to enable both; highly versatile step-mode bioprocessing of small and large proteins as well as established, isocratic SMB applications e.g. for oligomers.

The system flow path features PEEK tubing and a biocompatible valve block design that allows for the connection of 1 to 8 columns to accommodate increasingly intensified upstream titers, while reducing the clutter of rotary valves and external tubing. The system features six independently driven pumps that are each assigned to a process fluid, with each pump being user-replaceable among four sizes to cover a wide range of process scales. Built-in UV, conductivity, pH detectors enable complete process monitoring, while added features like the onboard sample injector, mixer, and gradient capability enable process design experiments as well.

The Octave BIO is the system to begin your process intensification journey, with tools and software to ease the transition.

The BIOController™ system control software provides a clean, user-friendly interface to execute and monitor your MCC process. This Windows™ compatible application features an intuitive, user-friendly interface that allows rapid mastery of its powerful functionality.

Methods are written with the PROComposer™ application and transferred into BIOController's Run Queue. The methods can be used with any size columns that match the capabilities of the Octave BIO because BIOController adjusts the time, volume and flow rate parameters based on the column dimensions and scaling selection entered in the Run Queue Manager. Each method is repeated within the sequence for a defined number of cycles, indefinitely or for a set time period.



	Pump Module
6	Octave BIO pumps
	Valve Module
1	Valve Block
1	Sample Injector
	Drawer Module
1	Reservoir Tray
	Display Module
1	System Status Display
	Sensor Module
4	Dual-channel UV Sensors
4	Conductivity Sensor
4	pH Sensors
1	Peak Collect Value
	User Interface, Software and Support
1	Windows™ 10 computer with monitor, keyboard and mouse
	PROComposer MethodWizard process design tool
	PROComposer method authoring software
	BIOController system control software

Specifications	
Dimensions (W/D/H)	137 × 51 × 98 cm
Weight	171 kg
Power requirements	100-120/220-240 VAC, 50/60 Hz
Valve pressure	At least 2 bar above process pressure
Flow rate range	up to 300 mL/min (2.4 mm valve block)
Inlets	6
Outlets	6
Columns	1-8
Maximum operating pressure	270 psi (18.6 bar)
UV sensors	4, LED, dual wavelenghts (255 & 280 nm)
Conductivity sensors	4, range 0-200 mS/cm
pH sensors	4, range 0-14
Modes	Step, batch, gradient, parallel, SMB

Ordering Information: Octave BIO

Part #	Description
MCC Benchtop	
0041102	Octave BIO Benchtop System 100 mL/min
0041103	Octave BIO Benchtop System 300 mL/min
0041101	Octave BIO Benchtop System 36 mL/min
0041100	Octave BIO Benchtop System 12 mL/min
MCC Benchtop Components	
0041107	Octave 12 mL/min pump
0041108	Octave 36 mL/min pump
0041109	Octave 100 mL/min pump
0041110	Octave 300 mL/min pump
0041104	Octave BIO 1 mm valve block
0041105	Octave BIO 1.6 mm valve block
0041106	Octave BIO 2.4 mm valve block


Octave® BIO
Octave® BIO
valve block

TOSOH

Production

Everything under control. Octave PRO provides:

- Single-use flow path design
- Real-time fluid control
- GMP-ready
- Process data access

Want to learn more? Visit our website.

Octave PRO

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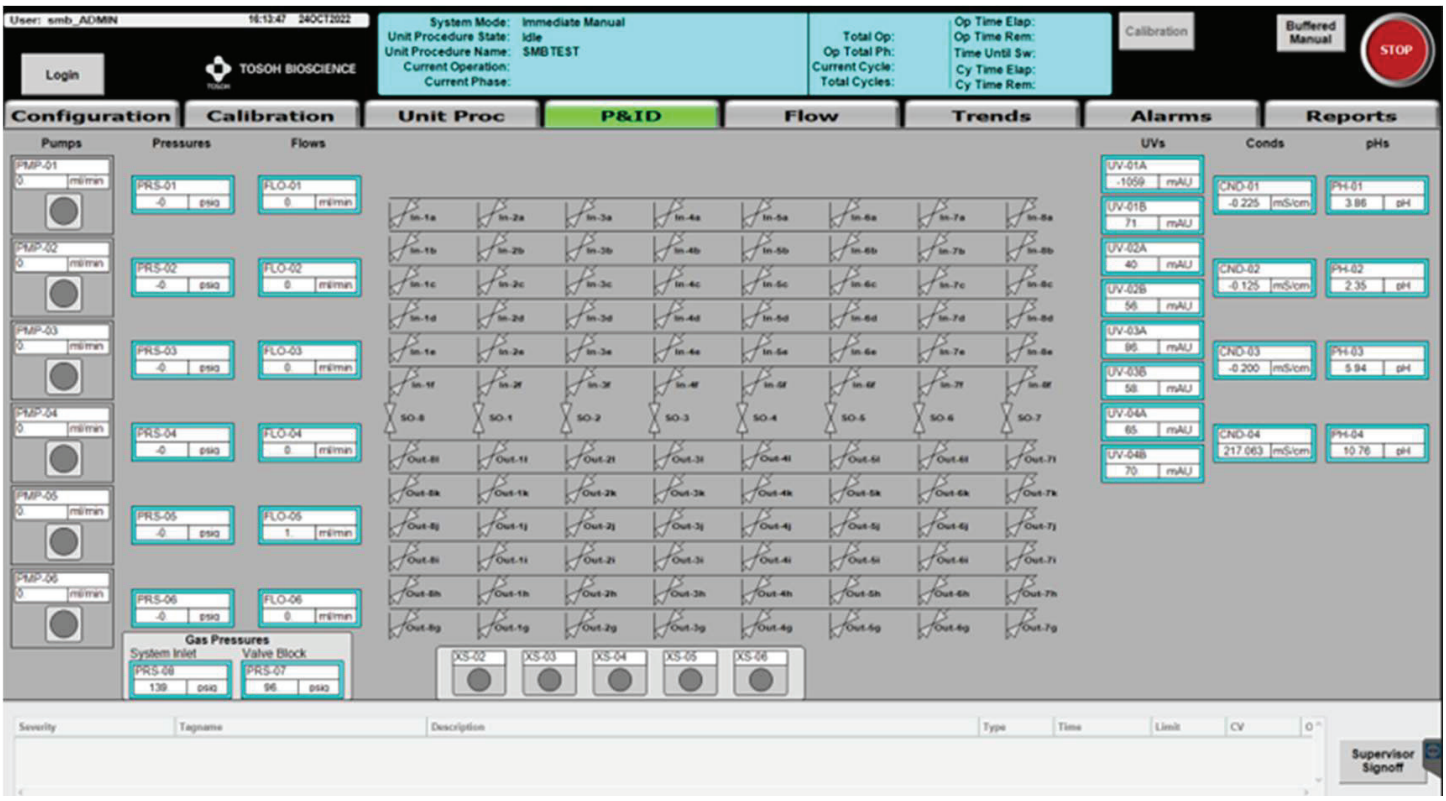
The Octave PRO from Tosoh Bioscience is a comprehensive multi-column chromatography (MCC) system for clinical production under GMP conditions. The system not only unlocks resin savings, buffer savings, and other tangible benefits that MCC can provide it will also make space available on your manufacturing site due to its small footprint design.

The system flow path features all bio-compatible tubing and valve block that allows for the connection of 1 to 8 columns to accommodate increasingly intensified upstream titers, while reducing the clutter of rotary valves and external tubing. The system features six independently driven pumps that are each assigned to a process fluid, with each pump being user replaceable among four sizes to cover a wide range of process scales. Built-in UV, conductivity, pH detectors enable complete process monitoring.

The Octave PRO is operated with GMP-compliant software. PROController™ system control software provides a clean, user-friendly interface to execute and monitor your MCC process. With the PROComposer method authoring software you are GMP-ready to seamlessly run methods developed on the Octave BIO in any scale on your Octave PRO system.



Overview and Comparison

	Octave BIO	Octave PRO
Project support	Development, Pre-clinical	Clinical, Commercial
Form factor	Bench top, portable	Skid, portable
Column capacity	1–8	1–8
Valve block	User-interchangeable; 3 channel diameters	Single use (SU)
Pumps	6	6; SU heads
Pump flow max.	12, 36, 100, 300 mL/min	2.5 L/min
Method software	PROComposer	PROComposer
Control software	BIOController	PROController
Data integrity	For Process Development	Ready for 21 CFR part 11 compliance
Bioreactor Size	Up to 150 L	Up to 2000 L
Processing Scale	Up to 500 g	Up to 20 kg

Specifications	
Dimensions (W/D/H) 210/89/218 cm	Weight 544 kg
Power requirements	100-120/220 VAC, 56/60 Hz
Valve pressure	At least 2 bar above process pressure
Max flow rate	2.5 L/min
Inlets	6
Outlets	6
Maximum operating pressure	6 bar
Pumps	6 quaternary diaphragm; single use heads
Pressure sensors	6; Single-use gauge tee [TS1]
Flow sensors	6; single-use; ultrasonic
Valve block	1; single-use combination containing 104 pnematic two-way valves
Outlet sensors	Four single-use combination UV/conductivity/pH; dual wavelength UV, CND range 0-200 mS/cm, pH range 0-14
Control system	PROComposer (PC; method authoring) PROController (PLC; GMP-validated)

Skid-based system for single-use biomanufacturing

Up to 150 L/h flow rates 6 bar

Rapid, economical processing of 50-2000 L feedstock

Up to eight columns

Four combination UV-conductivity-pH sensors

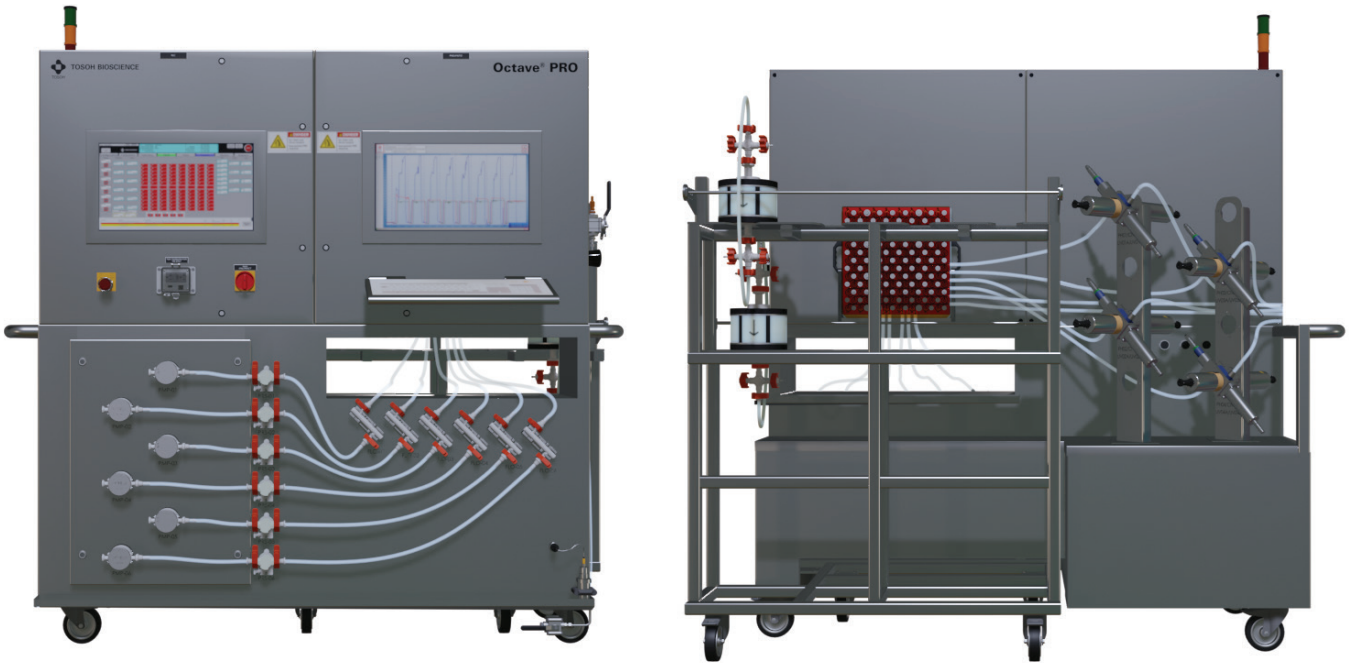
Compact footprint; convenient single-use flow path

Includes PROComposer, Method Creator and Method Wizard applications

Powerful, user-friendly GMP-compliant PROController control system

Specifications	Wetted materials (Single-use Flow Path)
Tubing	polybraided platinum cured silicone, silicone
Pump Head	polypropylene (PP), thermoplastic elastomer (TPE), ethylene propylene diene monomer (EPDM)
Flow Sensor	PP
Valve Block Assembly	USP class VI compliant acrylic, polyvinylidene fluoride (PVDF), polyfluoroalkoxy (PFA)
Optical/Conductivity/pH flow cell	quartz (UV transparent), EPDM, stainless steel 1.4435 (SS 316L), polyphenylsulfone (PPSU)

Contact your regional sales representative for ordering information.



TOSOH

Process Intensification

A holistic MCC solution! Complementing our Octave systems:

- SkillPak pre-packed columns
- Best-in-class TOYOPEARL® affinity resins
- PROComposer Method Wizard
- PROComposer Method Creator
- Service/Support

Want to learn more? Visit our website.

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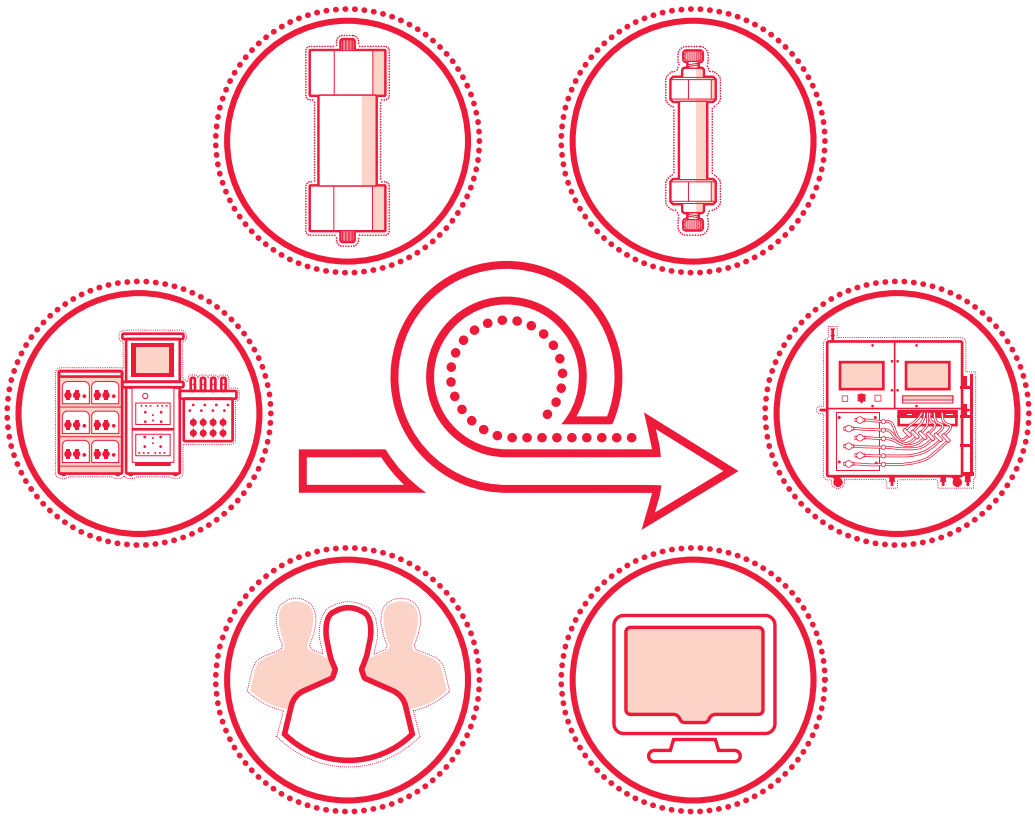
How to intensify your process – Tosoh's holistic MCC solution

By default, process development for traditional chromatography steps is done at the bench scale to minimize the necessary investment. To realize a large-scale purification, column dimensions and respective LC instrumentation are scaled-up to the intended product throughput, but this is done only after the requisite bench scale development.

Transferring processes to multi-column chromatography uses a similar approach in that intensification of batch processes with MCC is typically done at the bench scale. For this transition, Tosoh Bioscience provides both the versatile Octave BIO hardware to accommodate a wide range of process conditions, flexible software tools needed for the method development and method generation of an MCC process, as well as MCC optimized SkillPak BIO columns for method development and testing. SkillPak BIO columns come with both outstanding attributes (packing quality, stability and reproducibility) and a wide range of dimensions to enable its customers a seamless process development.

Scale up is executed after a proof of concept has been achieved of a well-defined MCC process with evident benefits. To address these needs, Tosoh Bioscience provides the GMP-ready Octave PRO solution, unified software tools for easy method scale-up, and the SkillPak PRO line of columns, which feature the same MCC attributes as the SkillPak BIO columns, in a scaled up, MCC optimized format.



SkillPak pre-packed columns

SkillPak are chromatography columns pre-packed with TOYOPEARL, TSKgel, or Ca^{++}Pure-HA process chromatography media. These columns have been designed to develop and scale-up purification processes for biomolecules, such as monoclonal antibodies, proteins, and oligonucleotides.

Whether you are screening resins, developing a purification method, working on the scale-up conditions of your batch or MCC process, or moving to manufacture under GMP conditions – the SkillPak columns are ready to use upon receipt. They offer ideal flow characteristics and reliable and reproducible performances for industrial downstream processing. Choose from these variants:

SkillPak for screening method development

SkillPak MAX for batch high-quality production under GMP conditions

SkillPak BIO for MCC feasibility operation

SkillPak PRO For MCC large-scale production under GMP conditions

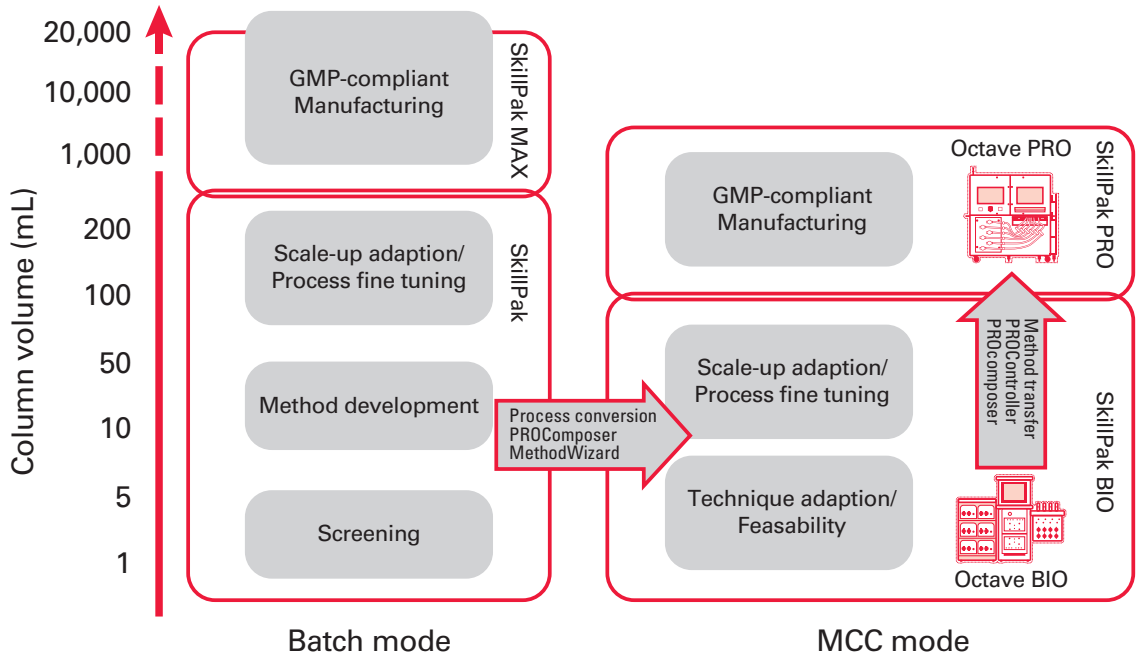
Among those four options, SkillPak BIO and SkillPak PRO hardware have been developed specifically to deliver the best experience and optimized process performance for multi-column chromatography applications.

SkillPak PRO column dimensions and use cases

Step	Dimensions	Volume	Flow rate at 0.5 min residence time
Process fine-tuning/ Manufacturing	8.0 cm ID × 5.1 cm	256 mL	512 mL/min
	14.0 cm ID × 5.1 cm	785 mL	1570 mL/min
	20.0 cm ID × 5.1 cm	1600 mL	3200 mL/min

SkillPak BIO column dimensions and use cases

Step	Dimensions	Volume	Flow rate at 0.5 min residence time
Screening/ Method development	0.8 cm ID × 2.0 cm	1 mL	2 mL/min
	1.6 cm ID × 2.5 cm	5 mL	10 mL/min
Technique adaptation/ Scale-up	1.6 cm ID × 5.1 cm	10 mL	20 mL/min
	2.5 cm ID × 5.1 cm	25 mL	50 mL/min
	5.0 cm ID × 5.1 cm	100 mL	200 mL/min



Available resins for SkillPak BIO and SkillPak PRO columns

Resin name	Application mode	Recommended to purifying...
TOYOPEARL AF-rProtein A HC-650F	Capture via Protein A	Monoclonal Antibodies
TOYOPEARL AF-rProtein L-650F	Capture via Protein L	Antibody Fragments
TOYOPEARL NH_2-750F	Polish via Anion exchange	Antibodies, antibody fragments, and other biomolecules
TOYOPEARL Sulfate-650F	Polish via Anion exchange	Antibodies, antibody fragments, and other biomolecules
TOYOPEARL GigaCap S-650S	Polish via (strong) Anion exchange	Viruses and vaccines, and other biomolecules
TOYOPEARL SuperQ-650S	High throughput capture, intermediate purification, and polishing	Therapeutic nucleic acids

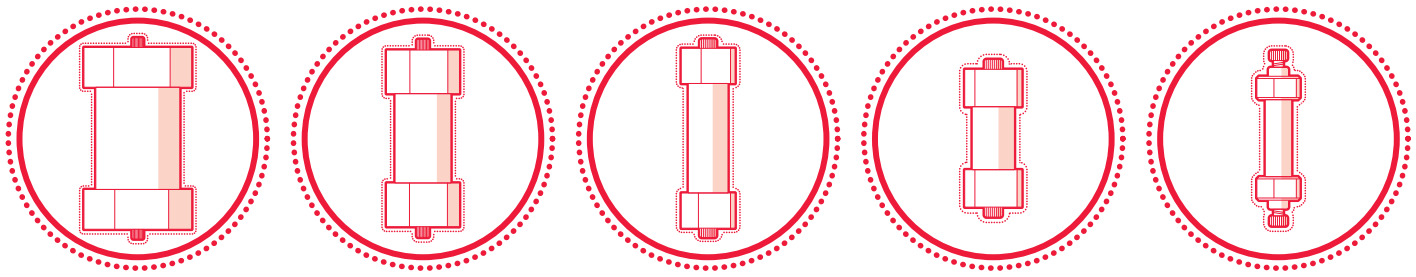
Please see our SkillPak brochure or website for ordering information.

Best-In-Class TOYOPEARL affinity resins

For multi-column chromatography, affinity chromatography processes present the most evident benefits from process intensification. As a result, another key component of Tosoh's comprehensive process intensification suite are TOYOPEARL best-in-class affinity resins, particularly TOYOPEARL AF-rProtein A HC-650F.

TOYOPEARL AF-rProtein A HC-650F is a high capacity Protein A resin for monoclonal antibody purification. The multi-point attachment between the ligand and base matrix results in excellent base stability for up to 200 CIP cycles with 0.1 mol/L NaOH. Achievement of high linear velocities at relatively low pressure enables high throughput processing at moderate pressure limitations. Improved mass transfer characteristics allow it to maintain a larger percent of its capacity at lower residence times relative to agarose base stable resins. Good pressure-flow characteristics and kinetics contribute to maintaining good capacity, particularly at low residence times.

Extended lifetime and caustic stability, relatively low pressure operation at high linear velocities, and good capacity at low residence times are all positive resin traits that make TOYOPEARL AF-rProtein A HC-650F a good fit for multi-column chromatography operation, where processes experience high capacity, and low residence time operation, with increased cycling for processing and cleaning.



Ease of process conversion and method transfer

Our unified PROComposer method-generating software package runs with any Windows-based PC and guides you from method development and proof of concept through to scale-up of highly efficient MCC processes.

The PROComposer Method Wizard simplifies conversion of batch to MCC methods. The Wizard provides tools to determine MCC process parameters, model a specific method, and compare batch and MCC process performance.

Moreover, methods developed with the Wizard saves methods in a format that can be opened, saved, and edited in the Tosoh Bioscience PROComposer Method Creator, which in turn can run on any Octave MCC system. As an added feature, batch methods can also be saved and edited in PROComposer format for running in single column mode.

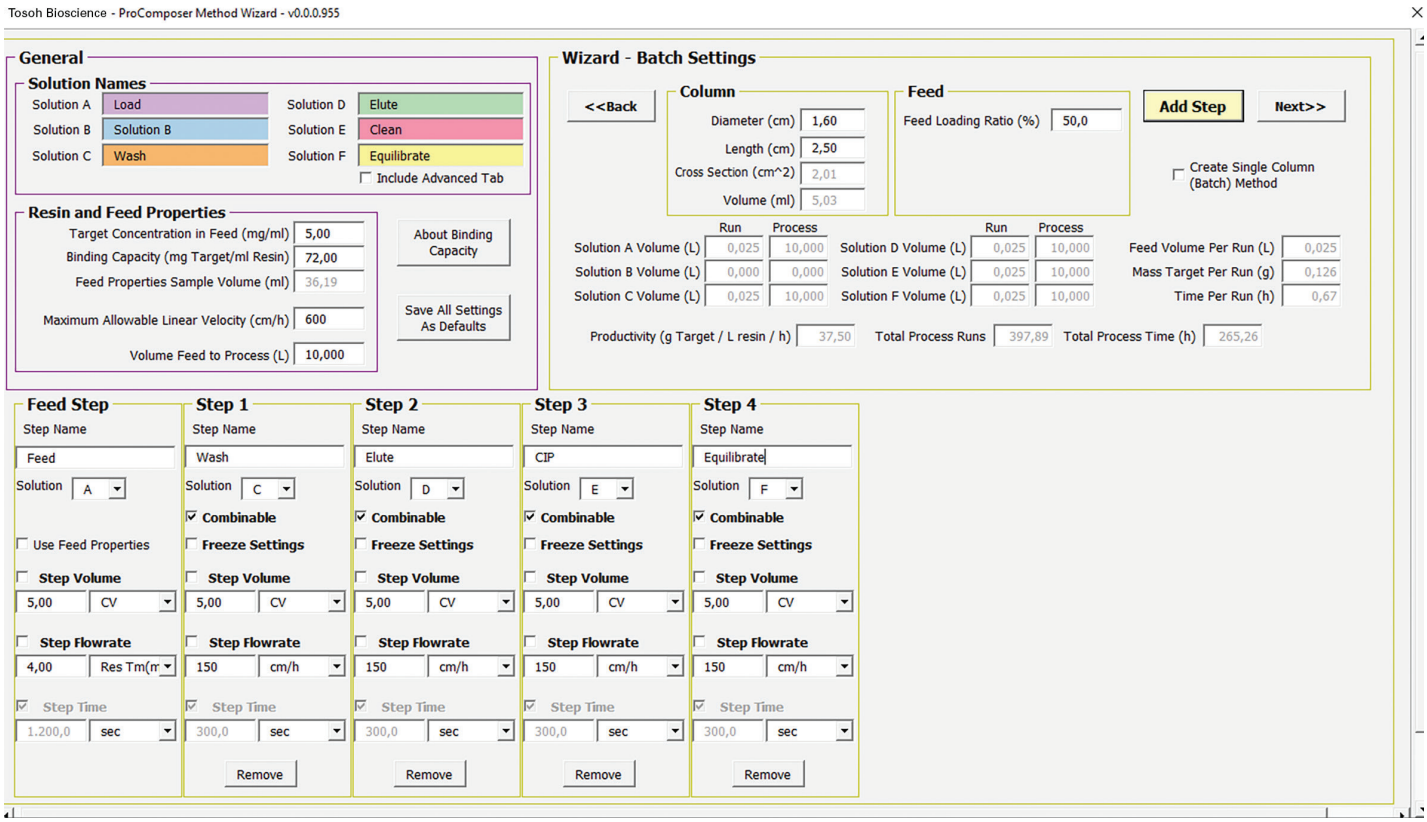
Parameter input for PROComposer Method Wizard

How to use the PROComposer Method Wizard

The Wizard is very easy to use. Simply enter the known parameters and protocol steps for your batch process, select the column size, number of columns in the loading zone and desired feed loading ratio for the MCC process, and the Wizard recommends the number of columns for MCC and compares the critical parameters of both processes.

How to adjust your process with PROComposer Method Wizard

Adjust column size, resin capacity, residence time, and maximum allowable flow velocity to optimize productivity, buffer usage, and/or process time.

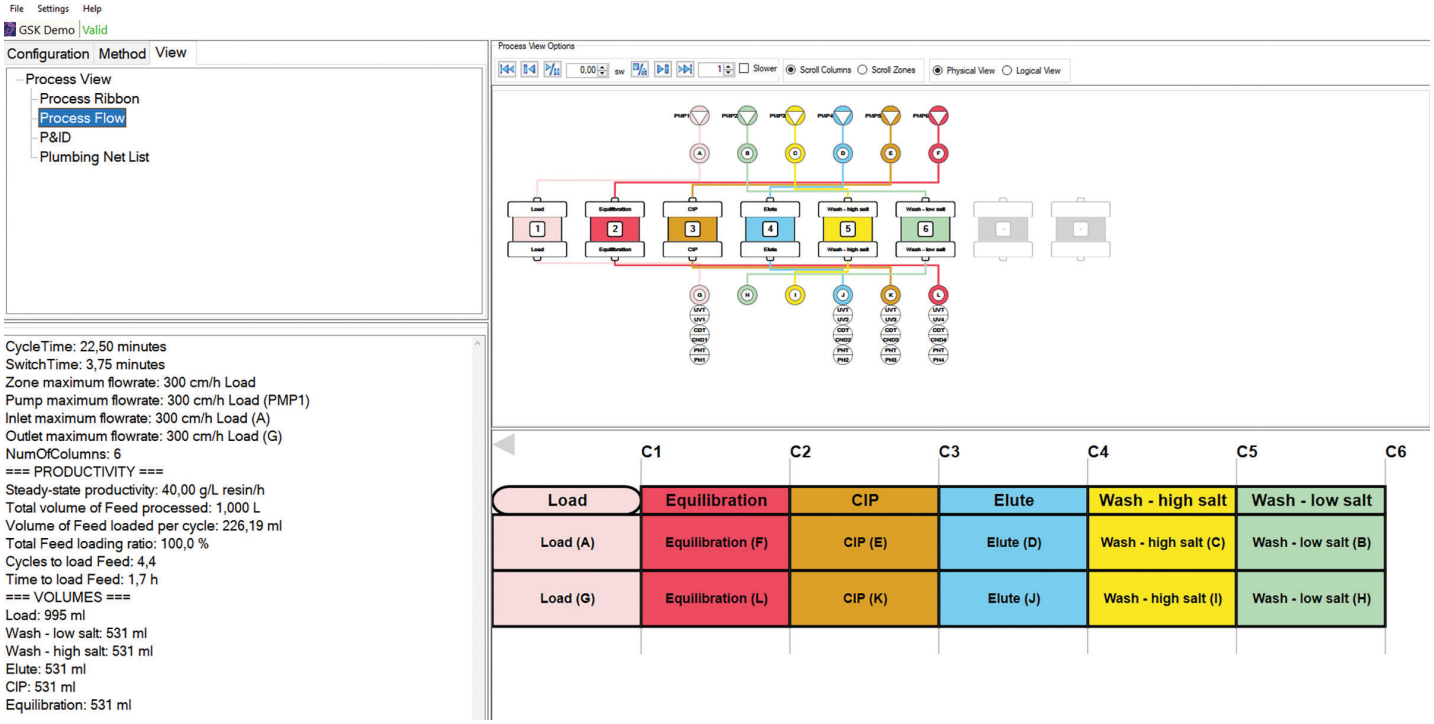


Method visualization of PROComposer Method Creator

The PROComposer Method Creator is used to create or edit multi-column chromatography and single column methods. The method files created with PROComposer on a Windows PC are transferred to the Octave BIO and Octave PRO Chromatography Systems for execution.

Methods created with PROComposer can be run with any size columns matched with our MCC Systems. The systems scale pump flow rates based on the column dimensions entered into the BIOController (Octave BIO) or PROController (Octave PRO) user interface.

Tosoh Bioscience provides all equipment and knowledge necessary to transfer your batch method to a continuous one. With our outstandingly flexible systems you will be able to adopt to a variety of purification methods and translate them to highly-efficient, GMP-compliant manufacturing of biomolecules. Contact us to learn more about our MCC solutions.



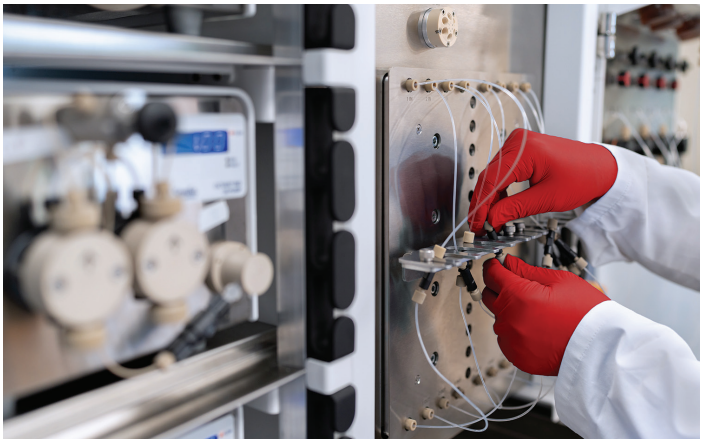
Services

Tosoh Bioscience is a globally operating company with locations around the world. Local service technicians are committed to provide the best quality support and service.

Our highest goal is to make your work with our systems and consumables as productive as possible. Therefore, regional service hotlines operated by Tosoh Bioscience staff with decades of chromatography experience enable fast management of any hurdles you might face.

Our service portfolio for MCC includes:

- Installation, familiarization, and training
- Maintenance
- Qualification (IQ, OQ, FAT, SAT)
- Repair on-site
- Extended warranty
- User education classes and visits
- Service agreements



Tiered Support Agreements

Level	Gold	Silver	Bronze
Prolonged warrenty status	Included	-	-
Preventive maintenance (annual visit)	Included	Included	Included
Additional discounts on	Consumable parts, Multiple planned PM visits	Warranty parts, Consumable parts, Multiple planned PM visits	Multiple planned PM visits
MCC user education	Included	Included	-
Non-scheduled service technical mission	Included	Included	-
Response time	5 business days onsite, Same/next business day remote support	10 business days onsite, Same/next business day remote support	Same/next business day remote support

Please visit our website to connect with your regional sales, service, and support contacts.

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