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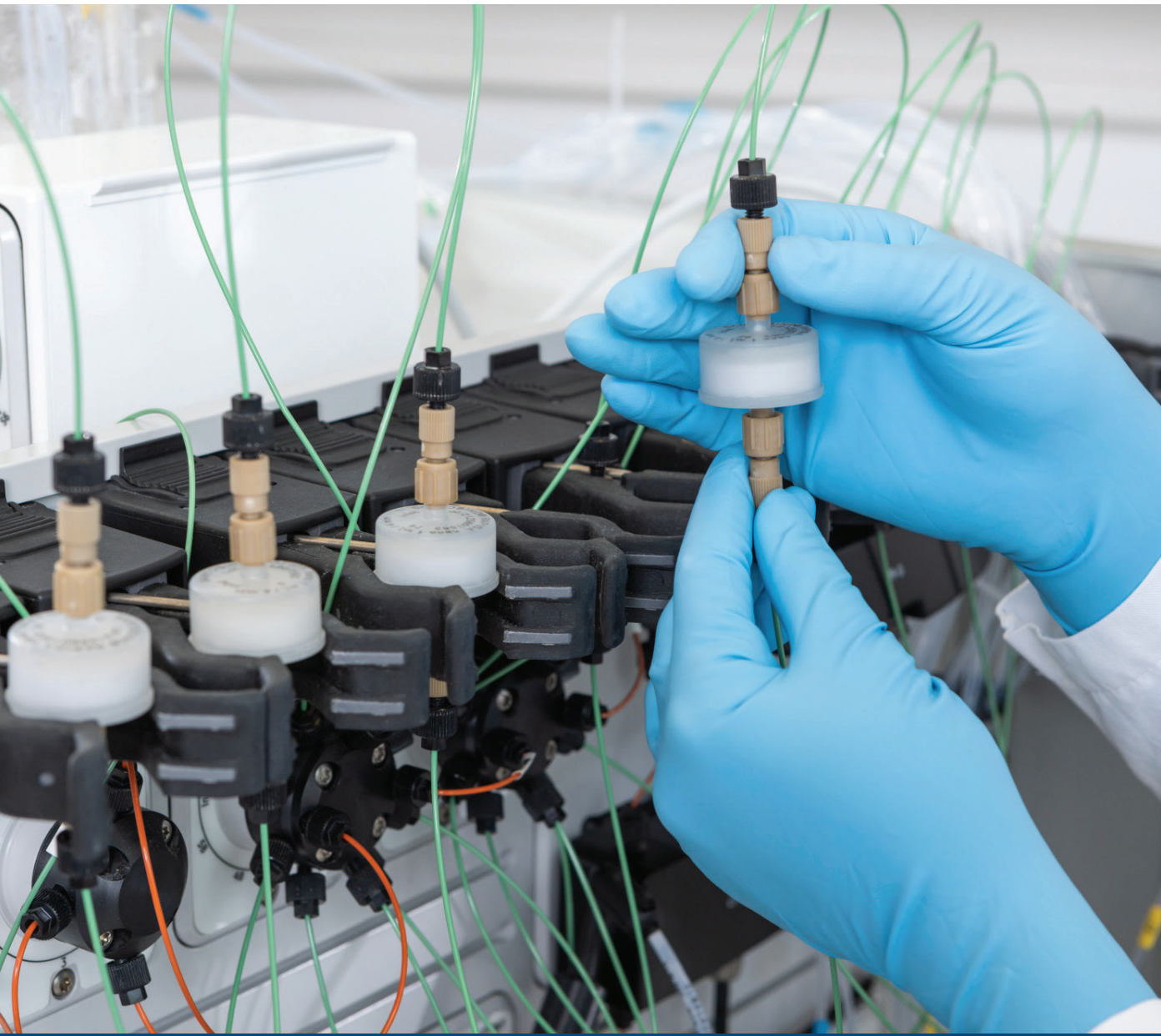

Intensified Antibody Purification with a Fully Membrane-Based Chromatography Workflow

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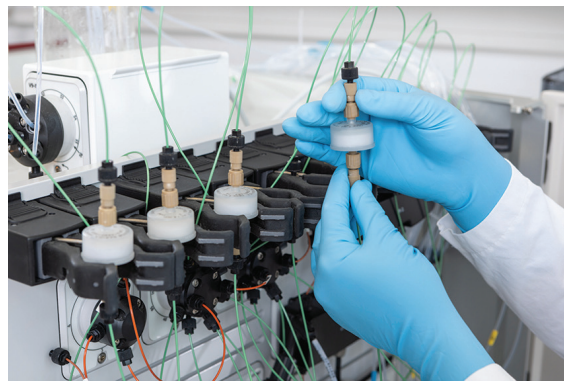
Monoclonal antibodies (mAbs) have become key therapeutics for treating diseases such as cancers and autoimmune disorders. Increasing demand for mAb therapies (at an 11% compound annual growth rate, CAGR) (**1**), rising cost pressure (**2–4**), and the need for better capacity utilization are key drivers for *process intensification* (PI), a holistic framework for maximizing the overall productivity of individual unit operations, manufacturing processes, and/or a biomanufacturing facility. Compared with conventional manufacturing approaches, PI enables more efficient and flexible processes, lower costs of goods (CoGs), and faster timelines within reduced facility footprints. Intensification also has direct benefits for facility sustainability by reducing water consumption, carbon and energy footprints, and disposable waste.

Many organizations have achieved PI in upstream operations (**5–12**). For instance, highly efficient cell lines and culture methods have helped companies to enhance process productivity and mAb titers (**9**). With increasing upstream yields, downstream process efficiencies become the next challenge, and we can expect the same level of intensification to happen over the next two to five years.

Downstream processing generally represents >50% of overall CoG in mAb manufacturing. Several intensification strategies are available to help downstream processes accommodate high upstream titers and increased manufacturing demand. Rapid-cycling chromatography (RCC) using membranes already has demonstrated strong productivity and cost benefits (**13–22**). Multicolumn chromatography (MCC) is the other leading technology for downstream PI. That method reaps similar benefits but at the cost of increased complexity (**22–25**). Beyond single unit operations, true downstream PI entails connection of processing steps to reduce process time and costs substantially (**19, 21, 26**).



An operator installs a Sartobind Rapid A membrane during downstream process development. (HTTPS://WWW.SARTORIUS.COM)

Ion-exchange and hydrophobic-interaction membrane chromatography are already established methods for mAb polishing steps. The introduction of protein A membranes for mAb capture now provides a compelling alternative to traditional resin-based chromatography — one that is applicable from process development and clinical production to commercial manufacturing. Unlike packed-bed resins, which are inherently limited by diffusional flow, membrane chromatography offers high permeability and high flow rates based on convective flow, a different mass-transfer mechanism. Numerous studies show that membranes consistently achieve product yields and product quality attributes that are comparable with those obtained by resins, yet membranes increase productivity and reduce costs by up to 60% in clinical production (**13–20**).

Materials and Methods

Tested Antibodies and Their Properties: For our comparison of mAb purification by membrane- and resin-based chromatography methods, two mAb types were expressed in Chinese hamster ovary (CHO) cells using standard fed-batch and perfusion culture techniques. Cell cultures were performed in

Table 1: Affinity chromatography in bind–elute mode; CV = column volume, MV = membrane volume

		Residence Time (min)		Volume	
Process Step	**Buffer**	**Membrane**	**Resin**	**Membrane**	**Resin**
Equilibration	50 mM tris-HAc, 150 mM NaCl, pH 7.4	0.2	5	20 MV	3 CV
Sanitization	0.2 M NaOH	0.2	10	25 MV	3 CV
Equilibration	50 mM tris-HAc, 150 mM NaCl, pH 7.4	0.1	5	30 MV	3 CV
Load	NA	0.2	5	20–40 mg/mL	30–60 mg/mL
Equilibration	50 mM tris-HAc, 150 mM NaCl, pH 7.4	0.2	5	45 MV	3 CV
Wash 1	50 mM NaAc-HAc, 1 M NaCl, pH 5.5	0.2	5	45 MV	3 CV
Wash 2	50 mM NaAc-HAc, pH 5.5	0.2	5	45 MV	3 CV
Elution	50 mM NaAc-HAc, pH 3.5	0.2	5	15 MV	5 CV
Strip	120 mM HAc	0.1	5	10 MV	3 CV
Equilibration	50 mM tris-HAc, 150 mM NaCl, pH 7.4	0.1	5	30 MV	3 CV

Table 2: Anion-exchange flow-through chromatography method; CV = column volume, MV = membrane volume

		Residence Time (min)		Volume	
Process Step	**Buffer**	**Membrane**	**Resin**	**Membrane**	**Resin**
Sanitization	0.5 M NaOH	0.2	10	40 MV	3 CV
Preequilibration	50 mM tris-HAc, 1000 mM NaCl, pH 5.5/7.5	0.1	5	20 MV	3 CV
Equilibration	50 mM tris-HAc, pH 5.5/7.5*	0.1	5	30 MV	3 CV
Load	Loading sample**	0.2	5	500–2000 mg/mL	100–200 mg/mL
Wash	50 mM tris-HAc, pH 5.5/7.5*	0.2	5	30 MV	3 CV
Strip	50 mM tris-HAc, 1000 mM NaCl, pH 5.5/7.5	0.1	5	30 MV	3 CV

* Buffer solution pH and conductivity were adjusted using 2 M tris and 2 M HAc to match the pH and conductivity of the loading sample.

** Buffer solution pH and conductivity were adjusted to pH 5.5 with conductivity <5.0 mS/cm or to pH 7.5 with conductivity <5.0 mS/cm using 2 M Tris and 2 M HAc, respectively.

Table 3: Cation-exchange bind–elute chromatography method; CV = column volume, MV = membrane volume

		Residence Time (min)		Volume	
Process Step	**Buffer**	**Membrane**	**Resin**	**Membrane**	**Resin**
Equilibration	50 mM NaAc-HAc, pH 5.5	0.2	5	30 MV	3 CV
Sanitization	0.5 M NaOH	0.2	10	40 MV	3 CV
Preequilibration	50 mM NaAc-HAc, 1000 mM NaCl, pH 5.5	0.2	5	20 MV	3 CV
Equilibration	50 mM NaAc-HAc, pH 5.5	0.2	5	30 MV	3 CV
Load	Loading sample	0.2	5	32 mg/mL	32 mg/mL
Wash	50 mM NaAc-HAc, pH 5.5	0.2	5	30 MV	3 CV
Elution	50 mM NaAc-HAc, pH 5.5 with variable conductivity*	0.2	5	30 MV	5 CV
Strip	50 mM NaAc-HAc, 1000 mM NaCl, pH 5.5	0.2	5	30 MV	3 CV

* Buffer solution conductivity was adjusted using 50 mM NaAc-HAc and 1000 mM NaCl (pH 5.5) to 16 mS/cm for membrane chromatography and 22 mS/cm for resin-based chromatography.

Table 4: Cation-exchange flow-through method; MV = membrane volume, RT = residence time (min)

Step	Buffer	RT	Volume
Sanitiz.	0.5 M NaOH	0.2	40 MV
Preequil.	50 mM tris-HAc, 1000 mM NaCl, pH 5.5	0.2	30 MV
Equilibr.	50 mM NaAc-HAc, pH 5.5*	0.2	30 MV
Load	Loading sample**	0.2	100–400 mg/mL
Equilibr.	50 mM NaAc-HAc, pH 5.5*	0.2	30 MV
Strip	50 mM NaAc-HAc, 1000 mM NaCl, pH 5.5	0.2	30 MV

* Buffer pH and conductivity were adjusted using 2 M tris, 2 M HAc, and 1 M NaCl to match the pH and conductivity of the loading sample.

** Buffer solution pH and conductivity were adjusted using 2 M tris, 2 M HAc, and 1 M NaCl to match the design of experiments.

Table 5: Design of experiments (DoE) setup for full factorial experiment; the two DoE responses assessed, yield and purity, were tested using size-exclusion high-performance liquid chromatography (SEC-HPLC).

Exper.	pH	Conductivity	Loading Capacity
1	4.5	20 mS/cm	100 g/L
2	6.0	10 mS/cm	400 g/L
3	6.0	20 mS/cm	100 g/L
4	4.5	10 mS/cm	400 g/L
5	4.5	10 mS/cm	100 g/L
6	5.25	15 mS/cm	250 g/L
7	5.25	15 mS/cm	250 g/L
8	6.0	20 mS/cm	400 g/L
9	5.25	15 mS/cm	250 g/L
10	4.5	20 mS/cm	400 g/L
11	6.0	10 mS/cm	100 g/L

Table 6: Parameter optimization for affinity membrane chromatography (bind–elute mode); MV = membrane volume

		Residence Time (min)		Volume (MV)	
Process Step	Buffer	Control	Optimized	Control	Optimized
Equilibration	50 mM tris-HAc, 150 mM NaCl, pH 7.4	0.2	0.1	20	7.5
Sanitization	0.2 M NaOH	0.2	0.1	25	20
Equilibration	50 mM tris-HAc, 150 mM NaCl, pH 7.4	0.1	0.1	30	15
Load	—	35 mg/mL at 0.1 min residence time			
Equilibration	50 mM tris-HAc, 150 mM NaCl, pH 7.4	0.2	0.2	45	7
Wash 1	50 mM NaAc-HAc, 1 M NaCl, pH 5.5	0.2	0.1	45	7
Wash 2	50 mM NaAc-HAc, pH 5.5	0.2	0.1	45	11.5
Elution	50 mM NaAc-HAc, pH 3.5	0.2	0.1	15	15
Strip	120 mM HAc	0.1	0.1	30	7

3-L My-control bioreactors (Applikon). Fed-batch cultures were harvested after 14 days; perfusion cultures were harvested continuously over 20 days. After centrifugation to remove cells and other debris, clarified supernatant underwent depth filtration (filter pore size of 0.2 µm, Sartorius). The molecules studied were **mAb1**, an immunoglobulin class G1 (IgG1) antibody expressed in fed-batch mode to titers of 3.52 g/L, and **mAb2**, an IgG4 antibody expressed in perfusion mode to titers of 1.213 g/L.

Chromatography System and Protein Concentration Analysis: Chromatographic purification was performed using ÄKTA Avant 150 and ÄKTA pure 150 systems operated with Unicorn software (all from Cytiva). We used a NanoDrop One microvolume ultraviolet-light (UV) spectrophotometer (Thermo Fisher) to determine protein concentrations.

Affinity Chromatography (AC) in Bind–Elute Mode: Harvested cell-culture fluid (HCCF) underwent AC using a Sartobind Rapid A Nano membrane (Sartorius) with a membrane volume (MV) of 1.2 mL. Purification using MabSelect SuRe LX resin (Cytiva) served as a reference control. Table 1 summarizes the chromatography conditions applied, including buffer properties and operation parameters.

Anion-Exchange (AEX) Chromatography in Flow-Through Mode: Samples for AEX study were prepared from the AC elution pool. We tested the separation performance of the Sartobind Q membrane (1 mL MV, Sartorius), with purification by Capto Q resin (Cytiva) serving as a control. Table 2 summarizes the AEX chromatography conditions and buffer properties.

Cation-Exchange (CEX) Chromatography — Bind–Elute Comparison Experiment: Samples used for our CEX comparison study were derived from the AC elution pool, material that we regarded as representing worst-case conditions for removing aggregates. Chromatographic separation was

Table 7: Parameter optimization for anion-exchange membrane chromatography in flow-through mode; MV = membrane volume

		Residence Time (min)		Volume (MV)	
Process Step	**Buffer**	**Control**	**Optimized**	**Control**	**Optimized**
Sanitization	0.5 M NaOH	0.2	0.1	40	20
Preequilibr.	50 mM tris-HAc, 1000 mM NaCl, pH 5.5	0.1	0.2	20	7
Equilibration	50 mM tris-HAc, pH 5.5	0.1	0.1	30	11.5
Load	Loading sample	2000 mg/mL at 0.1 min residence time			
Wash	50 mM tris-HAc, pH 5.5	0.2	0.2	30	20
Strip	50 mM tris-HAc, 1000 mM NaCl, pH 5.5	0.1	0.1	30	7

Table 8: Parameter optimization for cation-exchange membrane chromatography in flow-through mode; MV = membrane volume

		Residence Time (min)		Volume (MV)	
Process Step	**Buffer**	**Control**	**Optimized**	**Control**	**Optimized**
Sanitization	0.5 M NaOH	0.2	0.1	40	20
Preequilibr.	50 mM NaAc-HAc, 1000 mM NaCl, pH 5.5	0.2	0.2	30	7
Equilibr.	50 mM NaAc-HAc, pH 5.5	0.2	0.1	30	11.5
Load	Loading sample	Initial: 200 mg/mL at 0.2 min residence time Optimized: 202 mg/mL at 0.1 min residence time			
Wash	50 mM NaAc-HAc, pH 5.5	0.2	0.1	30	25
Strip	50 mM NaAc-HAc, 1000 mM NaCl, pH 5.5	0.2	0.1	30	7

performed using a Sartobind S membrane with a 1 mL MV (Sartorius). Purification based on Capto S ImpAct resin (Cytiva) served as a control. Table 3 summarizes the chromatography conditions.

CEX Chromatography — Flow-Through Purification Process: Samples used for the CEX flow-through–mode study also derived from the AC elution pool. Chromatographic separation leveraged a 1-mL MV Sartobind S membrane (Sartorius). Table 4 summarizes the chromatography conditions.

AC Dynamic Binding Capacity (DBC) Experiments: We took DBC measurements for the AC materials by loading HCCF onto a Sartobind Rapid A Nano membrane (1.2 mL MV) at residence times of 6, 12, 20, and 60 seconds. Flow-through fractions were collected during the loading phase, and antibody concentrations were monitored. Purification using MabSelect SuRe LX resin at a residence time of 300 seconds served as a control. DBC at 10% breakthrough ($DBC_{10\%}$) was calculated based on the amount of protein loaded when the ratio of the flow-through concentration (C) to the initial feed concentration (C_0) reached 0.1. Before sample loading, membranes and resins underwent equilibration with HCCF.

DBC measurements for CEX bind–elute processes were determined by loading the AC pool onto Sartobind S membranes (1 mL MV) at a residence time of 20 seconds. The CEX elution pool enabled calculation of the loading capacity, with a safety factor of 0.8. Capto S ImpAct resin, the control, was processed at a residence time of 300 seconds.

Design of Experiments (DoE) Evaluation for CEX in Flow-Through Mode: Process development for CEX membrane chromatography entailed a full factorial experiment approach with three factors at two levels. The factors investigated were conductivity (10.0–20.0 mS/cm), pH (4.5–6.0), and loading capacity (100–400 g/L). The responses evaluated were product yield and purity. Table 5 details the DoE setup.

Comparison of Process Performance at Varied Residence Times and Buffer Volumes for Membrane Processes: To improve the efficiency of the membrane-chromatography process, we optimized residence time and buffer volume (Tables 6–8).

Size-Exclusion High-Performance Liquid Chromatography (SEC-HPLC): We determined monomer and aggregate levels by measuring absorbance at 280 nm on an Agilent 1260 Series SEC-HPLC system. Samples were injected into a BioCore SEC column (300 Å, 5 µm, 7.8 mm × 300 mm, from NanoChrom) using 200 mM potassium phosphate and 250 mM potassium chloride (pH 6.2) as the running buffer. The flow rate was 0.5 mL/min. Monomer and aggregate proportions were estimated by integrating the peak areas of the early-eluting aggregate peak(s), late-eluting fragment peak(s), and the monomer peak.

Figure 1: Dynamic binding capacity at 10% breakthrough ($DBC_{10\%}$) for the Sartobind Rapid A membrane and MabSelect SuRe LX resin; mAb = monoclonal antibody

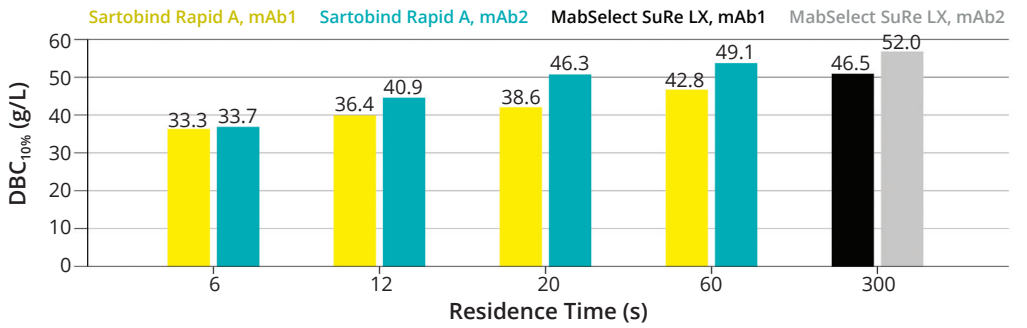


Table 9: Data used for scale-up projections with the Expert Chromatography Intensifier (ExCIT) tool; AC = affinity chromatography (bind–elute mode), AEX = anion-exchange chromatography (flow-through mode), CEX = cation-exchange chromatography (flow-through mode), $DBC_{10\%}$ = dynamic binding capacity at 10% breakthrough, HETP = height equivalent to a theoretical plate, mAb = monoclonal antibody, RT = residence time, QA = quality assurance

	Resin Process			Membrane Process		
Input Parameter	**AC**	**AEX**	**CEX**	**AC**	**AEX**	**CEX**
Bioreactor volume (clinical)	200 L			200 L		
mAb titers (clinical)	5 g/L			5 g/L		
Batches (clinical)	2 (toxicology + phase 1)			2 (toxicology + phase 1)		
Bioreactor volume (commercial)	2000 L and 5000 L			2000 L and 5000 L		
mAb titers (commercial)	5 g/L			5 g/L		
Batches per year (commercial)	40			40		
Target process time	12 hours	6 hours	5 hours	12 hours	6 hours	5 hours
Systems	Single-use system for clinical batches; multiuse system with cleaning in place for commercial					
Columns	Prepacked			Not applicable		
$DBC_{10\%}$	46.5 g/L	140 g/L	400 g/L	36.4 g/L at 0.2 min RT* 40 g/L at 0.5 min RT**	1000 g/L	400 g/L
Loading ratio	80%			80%		
Bed height	20 cm			4 mm		
RT	5–10 min (see Tables 1, 2, and 4)			0.1–0.2 min (see Tables 6–8)		
Yield	90%	99%	93%	90%	99%	93%
Life time	200 cycles			200 cycles		
Shelf life	3 years			2 years		
Bed compression factor	1.15			Not applicable		
Setup time	2 hours	2 hours	2 hours	1 hour	1 hour	1 hour
HETP test frequency	1/1 for clinical, 1/10 for commercial			Not applicable		
Labor requirement	6 operators, 1 QA staff member			6 operators, 1 QA staff member		
System cost amortization	10 years			10 years		
Buffer cost	€1.5/L			€1.5/L		
Labor cost	€50/hour for operators, €80/hour for QA staff			€50/hour for operators, €80/hour for QA staff		
Chromatography media cost	€15,000/L	€4000/L	€4000/L	€18,000/L	€6000/L	€6000/L

*RT used for 200-L and 2000-L bioreactors; **RT used for 5000-L bioreactors

Table 10: Product quality comparison for monoclonal antibodies (mAbs) purified by Sartobind Rapid A membranes or MabSelect SuRe LX resins; HCP = host-cell protein, hcDNA = host-cell DNA, HMWS = high–molecular-weight species, SEC-HPLC = size-exclusion high-performance liquid chromatography

	mAb1		mAb2	
Parameter	**Membr.**	**Resin**	**Membr.**	**Resin**
Yield (%)	89.6	89.6	96.5	94.2
HMWS (%)*	1.8	3.9	2.0	2.0
Monomer (%)*	98.2	96.1	98.0	97.8
HCP (ppm)	409	640	1248	1218
hcDNA (ppb)	2	<0.13	2	1

*HMWS and monomer content (%) was obtained using SEC-HPLC.

Based on inputs from laboratory-scale results, the ExCIT model can define **OPTIMAL** sizes for chromatography devices based on bioreactor size, mAb titer, chromatography-media dynamic binding capacity, and target process time.

Table 11: Comparison of host-cell protein (HCP) and DNA (hcDNA) clearance from samples of monoclonal antibody 1 (mAb1) under different loading conditions; notably, membranes showed equivalent reduction of host-cell proteins (HCPs) and DNA (hcDNA) to that achieved by resins. Based on those results, a two-step process with protein A capture and anion-exchange polishing would suffice to keep HCP and hcDNA levels within specifications.

	pH: 7.5, Conductivity: <5.0 mS/cm				pH: 5.5, Conductivity: <5.0 mS/cm			
	Membrane			Resin	Membrane			Resin
Loading capacity (mg/mL)	1000	1400	2000	140.1	1000	1400	2000	140.7
Yield%	NA*	NA*	99.8	98.5	NA*	NA*	99.7	100.0
HCP (ppm)	10	10	11	10	63	70	72	63
hcDNA (ppb)	<0.1	<0.1	<0.1	<0.1	<0.1	0.2	<0.1	1

*HCP and hcDNA levels were analyzed at the designated loading capacities. Product yield was not evaluated in this study. The loading sample used for this study contained HCPs at 525 ppm and hcDNA at 5 ppb.

Titer Assay: Flow-through samples for both mAb types underwent titer determination using high-performance protein A affinity chromatography. Cell-culture supernatants were centrifuged at 13,000*g* for 10 minutes. BioCore PrA-HPLC columns (15 µm, 2.1 × 30 mm, NanoChrom) were equilibrated with 50 mM sodium phosphate and 150 mM NaCl (pH 7.0), then loaded with supernatant. After column washing with 10 column volumes (CVs), antibodies eluted linearly with 0.1 M glycine–HCl (pH 2.5). To detect the sample, we plotted a standard curve using six pure protein samples with concentrations ranging from 0.2 to 5.0 g/L. Titer calculations were based on the area of the elution peak.

Host-Cell Protein (HCP) Assay: We applied an enzyme-linked immunosorbent assay (ELISA) kit from Cygnus Technologies to detect HCPs. In total, 50 µL of mAb sample and 100 µL of α-anti-CHO antibody–horseradish peroxidase (HRP) conjugate were added to a coated 96-well strip plate, which we incubated at 500 rpm for two hours. Then, each well was washed with 300 µL of 1× washing buffer four times. Subsequently, we added 100 µL of tetramethylbenzidine (TMB) to each well, and the plate was incubated away from light for 30–60 minutes. Finally, we added 100 µL of stop solution, and wells were analyzed in a microplate reader for optical density (OD) at 450–650 nm.

Nonreducing Sodium Dodecyl Sulfate–Capillary Electrophoresis (SDS-CE): For each sample, we prepared a 75-µL reaction mixture comprising 70 µL of low-pH phosphate sodium dodecyl sulfate sample buffer and 5 µL of 250 mM iodoacetamide (IAM). From that, 25 µL of solution was transferred to a microsample tube. Mixtures were incubated at 70 °C for 10 minutes, cooled to room temperature, and centrifuged until no visible liquid remained on the tube caps. Finally, samples were transferred to microvials.

Expert Chromatography Intensifier (ExCIT) Tool: We applied the ExCIT model (developed by Sartorius) to laboratory-scale results to compare membrane and resin performance, bind–elute and flow-through modes, and batch and connected workflows when projected to larger-scale production at 200 L, 2000 L, and 5000 L bioreactor volumes at titers of 5 g/L. Table 9 shows the parameters applied. With such inputs, the model can define

Table 12: Clearance of host-cell proteins (HCPs), host-cell DNA (hcDNA), protein A residue, and aggregates at the same loading capacity; samples were derived from protein A elution pools from monoclonal antibody 1 (mAb1) samples. (CE-NR = nonreducing capillary electrophoresis, CEX = cation-exchange chromatography, LMW = species of low molecular weight, SEC-HPLC = size-exclusion high-performance liquid chromatography)

Parameter	Membrane	Resin
Loading capacity	32 mg/mL	32 mg/mL
Yield (%)	93.2	97.5
SEC-HPLC monomer (%)	99.3	98.2
CE-NR monomer/ LMW (%)	98.1/1.7	98.0/1.7
CEX acidic/main/ basic (%)	21.3/72.3/6.3	21.0/71.1/7.9
Protein A (ppm)	0.1	0.3
HCP (ppm)	11	8
hcDNA (ppb)	2	<0.2

Table 13: Design of experiments (DoE) study results; monomer content was assessed using size-exclusion high-performance liquid chromatography

	Factors			Responses	
	pH	Conductivity (mS/cm)	Capacity (g/L)	Yield (%)	Monomer (%)
Load	—	—	—	—	81.8
1	4.5	20.0	100	69.0	98.8
2	6.0	10.0	400	91.6	87.4
3	6.0	20.0	100	93.4	85.9
4	4.5	10.0	400	86.3	85.1
5	4.5	10.0	100	57.6	87.6
6	5.25	15.0	250	89.4	90.2
7	5.25	15.0	250	89.0	90.1
8	6.0	20.0	400	97.4	83.2
9	5.25	15.0	250	88.2	89.7
10	4.5	20.0	400	91.0	87.2
11	6.0	10.0	100	73.6	97.9

optimal sizes for chromatography devices based on bioreactor size, mAb titer, chromatography-media DBC, and target process time. The recipes established in our study were entered into the ExCIT program to calculate cycle times, number of cycles required, and buffer consumption. Using such data, the model also can calculate processing times, productivity, throughput, and CoGs for entire chromatography workflows, including costs of resins, membranes, systems, labor, validation, preparation, and cleaning in place (CIP).

Results

AC with Sartobind Rapid A Membrane — DBC and Product Quality Performance: DBCs of Sartobind Rapid A membranes were determined based on 10% breakthrough at different residence times. As shown in Figure 1, $DBC_{10\%}$ increased with residence times, ranging from 33.3 to 49.1 g/L at residence times of 6, 12, 20, and 60 seconds. At 60-second residence times, Sartobind Rapid A membranes exhibited binding capacities comparable with those of MabSelect SuRe LX resin. In addition, product quality and yield were consistent across both materials (Table 10).

AEX Chromatography with Sartobind Q Membranes — Loading pH Study: This study evaluated the effects of loading pH and loading capacity on Sartobind Q membrane removal of HCPs and host-cell DNA (hcDNA) from mAb 1 samples. As shown in Table 11, increasing the loading capacity from 1000 mg/mL to 2000 mg/mL had no significant impact on HCP and hcDNA clearance. Notably, loading at pH 7.5 resulted in significantly enhanced HCP and hcDNA removal compared with loading at pH 5.5. Despite higher loading, Sartobind Q membrane removal of HCPs and hcDNA was comparable to that achieved by conventional column chromatography.

CEX Chromatography with Sartobind S Membranes — Loading Capacity and Product Quality Performance in Bind–Elute Mode: We evaluated CEX-chromatography loading capacity by measuring the amount of mAb 1 recovered through high-salt elution after sample overloading. At a residence time of 20 seconds, with pH 5.5 ± 0.1 and conductivity ≤5.0 mS/cm, the binding capacity of the Sartobind S membrane was substantially lower than that of the CEX resin operated at a residence time of 5 minutes (Figure 2).

At the same loading capacity, membrane and column chromatography showed comparable eluate quality and impurity removal (e.g., of HCPs, hcDNA, leached protein A, and aggregates) (Table 12).

Process Development for CEX Membrane Chromatography in Flow-Through Mode: Given CEX membrane chromatography's inherently low binding capacity compared with that of conventional resin-based systems, we developed a flow-through process to exploit weak electrostatic interaction between the membrane and HCPs. Loading-sample pH and conductivity influenced such interactions significantly, affecting the balance between impurity removal and product recovery.

To evaluate those parameters' impacts systematically, we conducted a full-factorial DoE study, with pH, conductivity, and loading capacity selected as key experimental factors. Because the primary objective of CEX chromatography is to

Table 14: Performance and product-quality profiles for initial and optimized membrane-chromatography processes; AC = affinity chromatography, AEX = anion exchange, CE-NR = nonreducing capillary electrophoresis, CEX = cation exchange, HCP = host-cell protein, hcDNA = host-cell DNA; NA = not applicable, SEC-HPLC = size-exclusion high-performance liquid chromatography

Format	Process Type	Yield (%)	SEC-HPLC Monomer (%)	CEX Acidic/ Main/Basic (%)	CE-NR Monomer/ LMW (%)	HCP (ppm)	hcDNA (ppb)	Protein A (ppm)
AC	Control	57	98.7	29.2/64.0/6.9	97.7/2.4	604	2	0.1
	Optimized	63	98.7	30.8/62.5/6.6	96.5/3.5	1277	6	0.1
AEX	Control	99.7	NA	NA	NA	72	<0.1	2
	Optimized	100.1	NA	NA	NA	79	<0.1	1
CEX	Control	92.6	98.6	23.0/70.8/6.2	98.3/1.7	40	<0.6	1
	Optimized	89.4	98.5	22.7/70.0/7.4	98.2/1.8	43	<1	1

Figure 2: Comparison of loading capacities at 10% breakthrough

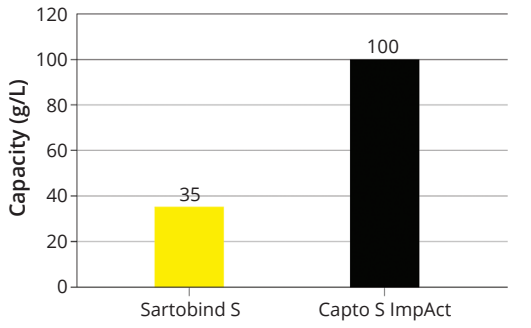


Table 15: Quality data from the full-membrane process comprising affinity chromatography (AC) for antibody capture and anion-exchange (AEX) and cation-exchange (CEX) polishing steps performed in series (PP = post-polishing); to improve the aggregation-control capability of the CEX membrane, the loading sample was adjusted to pH 5.47, and conductivity was set to 11.5 mS/cm. The low-pH and high-conductivity loading conditions reduced the AEX step's ability to remove host-cell proteins (HCPs). (CE-NR = nonreducing capillary electrophoresis, hcDNA = host-cell DNA, SEC-HPLC = size-exclusion high-performance liquid chromatography)

Pool	CE-NR Monom.	SEC-HPLC Monom.	HCP (ppm)	hcDNA (ppb)	Prot. A Residue	Overall Yield
AC	97.7%	97.5%	894	<2	<0.26	≈80%
PP	98.3%	98.9%	66	<3	<0.49	

control product aggregates, monomers and yield (from SEC-HPLC) were our key response variables. Table 13 summarizes results from those experiments. Data fitting and analysis were conducted in JMP software to generate predictive profilers. Contours and parameter ranges were generated based on different process-desirability values (Figure 3).

We chose two process-parameter ranges based on distinct purification purposes:

• When prioritizing aggregate reduction, optimal parameter ranges for pH, conductivity, and loading capacity were 5.8–6.0, 9.6–11.8 mS/cm, and 75–150 g/L, respectively. Under those conditions, the range of aggregate-control capability was 12.2–17.2%, and product yield exceeded 67% (Figure 4).

• When prioritizing product yield, the optimal ranges for pH, conductivity, and loading capacity were 5.8–6.0, 17.0–20.0 mS/cm, and 225–400 g/L. Under those conditions, product yield exceeded 95%, and aggregate control capability was 1.9–6.4% (Figure 5).

Process Steps Comparison: Given the relatively high buffer consumption associated with protein A membrane chromatography, we undertook process optimization to enhance process efficiency and reduce raw-material use. Operational experience and experimental data generated during process development informed our optimization of buffer volumes and conditions for each chromatographic step. Specific optimization strategies are detailed in the methods section.

Compared with the original workflow, the optimized membrane-chromatography process demonstrated comparable product quality and process performance without compromising critical product attributes (Table 14).

Fully Membrane-Based Chromatography Workflow: We performed a full-membrane chromatography process based on the process parameters described above (Tables 6–8). Based on HCCF mAb titers and predefined membrane cycle numbers, we calculated loading capacities for the different membrane types: 32 mg/mL for AC, 504 mg/mL for AEX, and 290 mg/mL for CEX. The process begins with AC, followed by low-pH virus inactivation and depth filtration (using an H2HP device from Cobetter). Samples were adjusted to pH 5.47 and conductivity 11.48 mS/cm before polishing. AEX and CEX chromatography membranes operated in series without intermediate pH adjustment. Figure 6 illustrates the process concept. Table 15

Figure 3: Prediction profiler in JMP software, with pH value, conductivity, and loading capacity as parameters

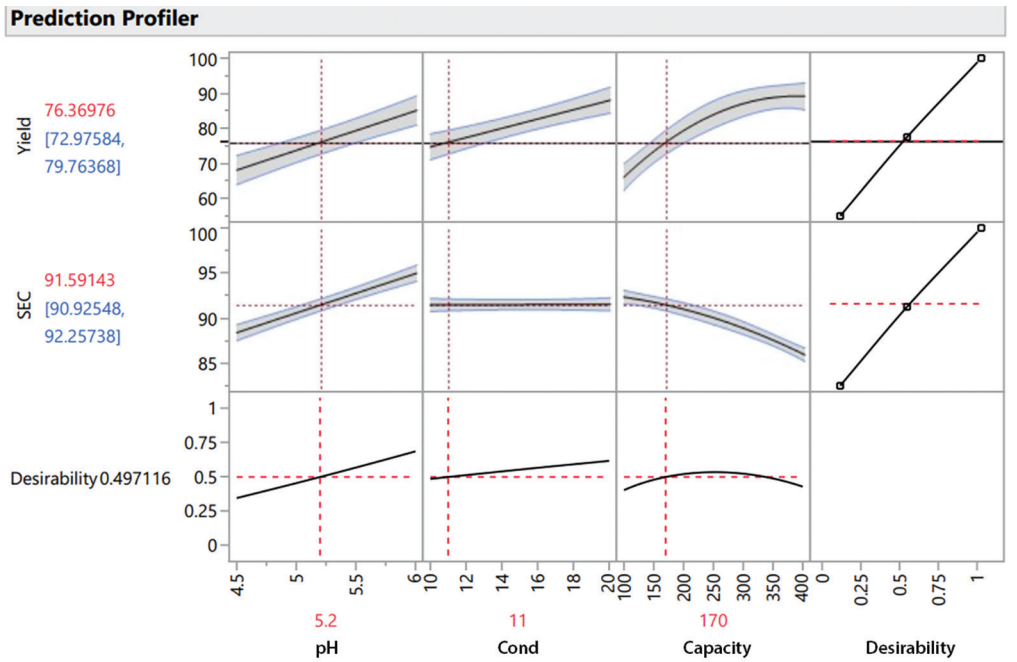


Figure 4: Contour profiler in JMP software illustrating parameter ranges for monomer levels (assessed by size-exclusion high-performance liquid chromatography, SEC-HPLC) and protein yield needed to prioritize purity improvement; responses were set to yields of >67% and monomer content of >94%. The red area shows the acceptable range of parameters. Therein, maximum and minimum predicted yields were 83% and 67%, respectively. Maximum and minimum levels for monomer content were 99.0% and 94.0%. Compared with the monomer content in the loading sample (81.8%), monomer improvement ranged 12.2–17.2%.

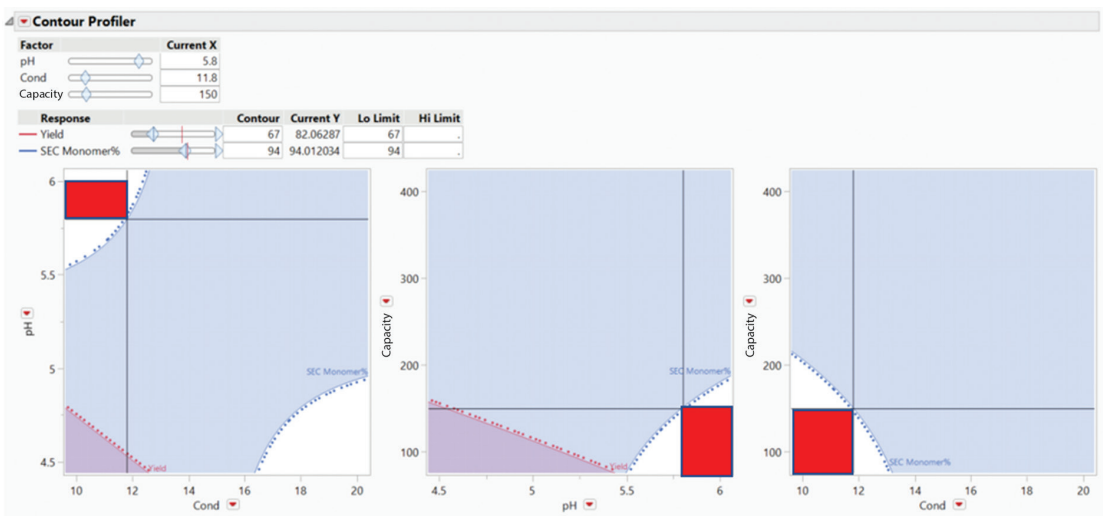


Figure 5: Contour profiler in JMP software illustrating optimal parameter ranges for monomer content (as determined by size-exclusion high-performance liquid chromatography, SEC-HPLC) and protein yield needed to prioritize high step yield; responses were set to yields of >95% and monomer levels of >80%. The red area shows the acceptable range of parameters. Therein, the maximum and minimum predicted yields were 97% and 95%. The highest and lowest predicted monomer levels were 88.2% and 83.7%. Compared with the loading sample's monomer content (81.8%), monomer improvement ranged 1.9–6.4%.

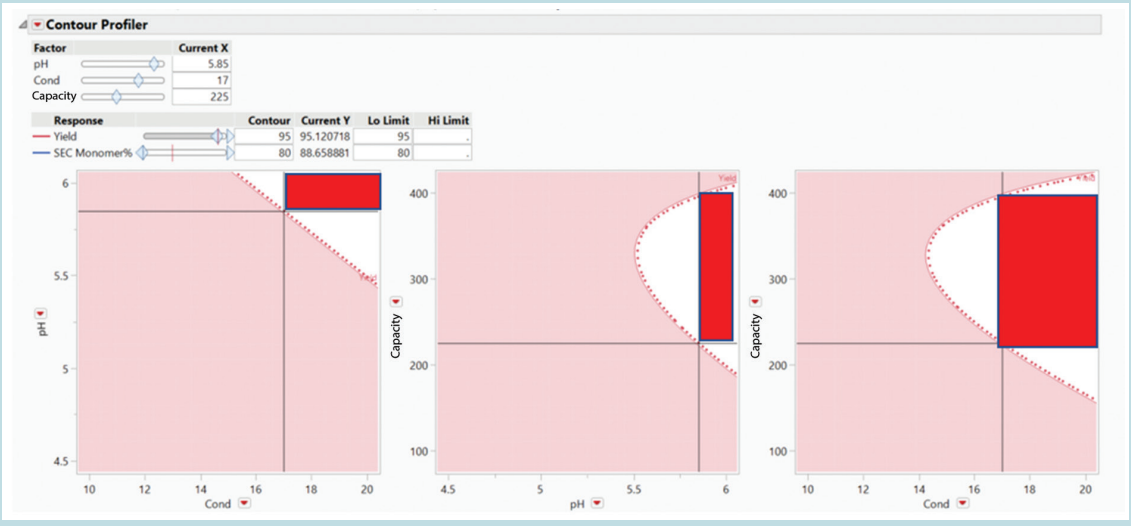
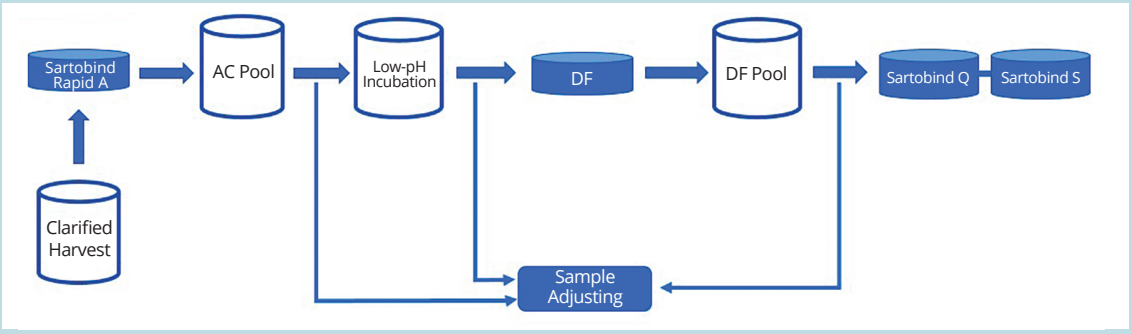


Figure 6: Full-membrane process concept; AC = affinity chromatography, DF = diafiltration



lists quality data from the CEX flow-through pool. The combined yield of all steps was about 80%.

Discussion

Scale-Up and Cost Modeling: Implementing a fully integrated membrane chromatography process comprising a bind–elute capture step and two flow-through polishing steps reduces buffer consumption and process time while meeting product purity levels (**17**). In this study, we optimized our process recipe and evaluated the cost, productivity, yield, and product quality of a full-membrane chromatography workflow. The recipe involved mAb capture using a Sartobind Rapid A membrane and subsequent double flow-through polishing steps using Sartobind Q (AEX) and Sartobind S (CEX) membranes. We evaluated product purity through analyses of HCPs, hcDNA, aggregates, and fragments, and results from the full-membrane workflow were comparable to those from traditional resin-based processes.

Although several studies have demonstrated the benefits of PI with membrane chromatography, an intensification journey is difficult to start when companies have their own platforms and infrastructures for established drug products. The cost of changes, the uncertainty about their benefits, and efforts for regulatory filing are the main barriers to overcome. There are multiple ways to intensify a purification workflow, such as RCC with membranes, MCC with membranes or resins, and connected multistep chromatography (MS-MCC) (**20–28**). Choosing the right strategy from the start will ensure that the intensification journey is worth the effort and achieves the expected cost, time, productivity, and throughput gains.

Figure 7: Comparison of chromatography media volumes, cycles, and process times for resin and membrane batch processes at 200-L bioreactor scale

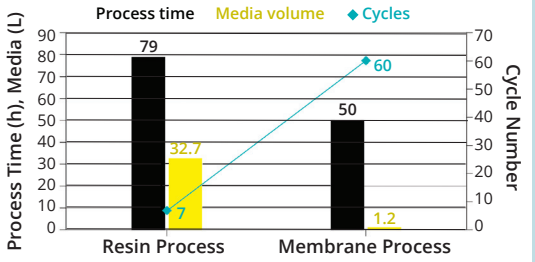


Figure 8: Comparison of total chromatography cost of goods for resin- and membrane-based processes (two production batches) at 200-L bioreactor scale, broken down by media, buffers, hardware, labor, and flow kits

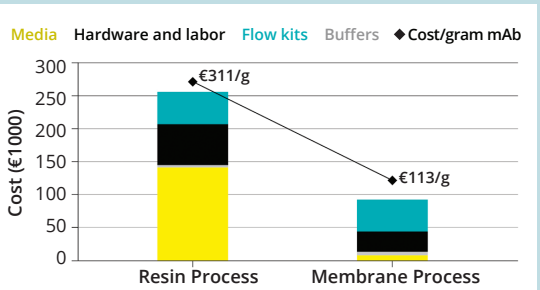
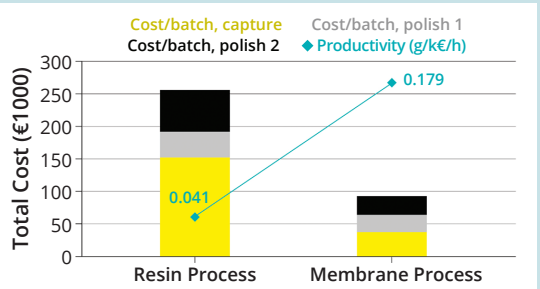


Figure 9: Comparison of total cost of goods for resin- and membrane-based batch processes (two production batches) at 200-L bioreactor scale, broken down by chromatography steps and productivity



Our laboratory-scale study and scale-up model show that implementing a full-membrane chromatography workflow for downstream purification of mAbs can be a **SIGNIFICANT** cost-saving alternative to traditional resin-based steps during process development, clinical production, and commercial manufacturing.

Based on process parameters from the laboratory-scale study, we used the ExCIT tool to model scale-up of a full-membrane chromatography process for clinical batches of 200 L at a mAb titer of 5 g/L and for larger commercial batches of 2000 L and 5000 L at 5 g/L.

Clinical Production — Two Production Batches, 200-L Bioreactor at 5 g/L: Antibodies expressed at 5 g/L in a 200-L bioreactor could be purified using Resolute Flowdrive 900 L/hour systems, Sartobind Rapid A membranes for capture, and Sartobind Q and S membranes for double flow-through polishing. All three steps would use 1.2 L of membrane material over 60 cycles. By comparison, a traditional process would require 32.7 L of resin over seven cycles. The full-membrane chromatography process would enable purification of clarified harvest in 50 hours, compared with 79 hours for a resin process (Figure 7).

Figure 8 details total costs per batch for production of two clinical batches. Chromatography cost per gram of mAb produced would be reduced from €311/g with a traditional resin process to €113/g for a full-membrane process. Productivity (calculated in terms of grams purified per thousand euros per hour) also would increase from 0.041 g/k€/h for resins to 0.179 g/k€/h for membranes (Figure 9).

Commercial Production — 40 Production Batches per Year, 2000-L Bioreactor at 5 g/L: Antibodies expressed in a 2000-L bioreactor at a titer of 5 g/L could be purified in a connected workflow using the Resolute BioSC system to connect the capture step (with a Sartobind Rapid A membrane), low-pH virus inactivation step, and double flow-through polishing steps (with Sartobind Q and S membranes). The resulting process would use only 9 L of membrane material running at 82 cycles across all three steps. By comparison, a batch resin-based process would require 170 L of resin material and eight cycles for the three steps. The full-membrane connected chromatography process would enable purification of clarified harvest in 42 hours, compared with 79 hours for a batch resin process (Figure 10).

Figure 11 shows total costs per batch to produce 40 commercial batches per year. Chromatography costs per gram of mAb for large-scale production is projected to reach about €11/g for both the traditional resin-based process and full-membrane workflow.

Figure 10: Comparison of chromatography media volumes, cycles, and process times for a resin-based batch process and a connected membrane-based process at 2000-L bioreactor scale

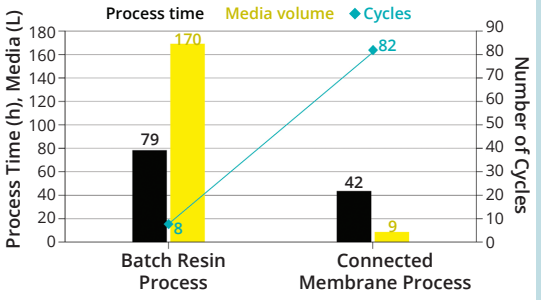


Figure 11: Comparison of total chromatography cost of goods for a resin-based batch process and connected membrane-based process at 2000-L bioreactor scale (40 batches per year), broken down by media, buffers, hardware, labor, and cleaning in place (CIP)

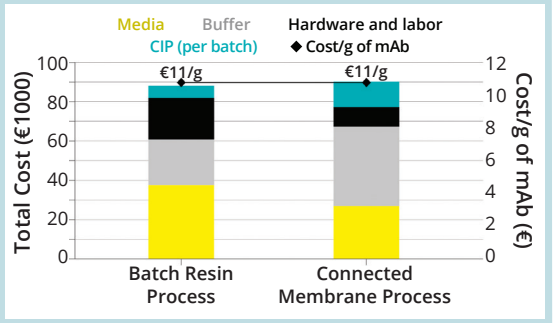
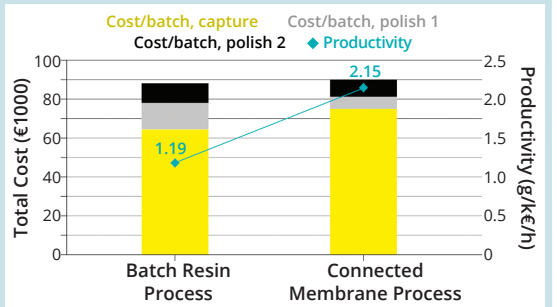


Figure 12: Comparison of total chromatography cost of goods (CoG) broken down by step and productivity for a resin-based batch process and a connected membrane-based process at 2000-L bioreactor scale



Productivity would increase from 1.19 g/k€/h for resins to 2.15 g/k€/h for membranes (Figure 12) because of the time reduction from 79 to 42 hours (Figure 10). In this case study, we expect the time reduction obtained with a connected membrane process to increase the potential number of production batches per year from 40 to >75.

Commercial Production — 40 Production Batches per Year, 5000-L Bioreactor at 5 g/L: Material from a 5000-L bioreactor at a titer of 5 g/L could be purified in a connected workflow equivalent to the 2000-L scale using only 22 L of membrane material running at 80 cycles across all three steps. For this large scale, residence time for the Sartobind Rapid A membrane would increase from 0.2 to 0.5 min, and DBC would rise from 36.4 to 40 g/L. In comparison, a batch process would require 473 L of resin running at seven cycles across the three steps. The connected full-membrane chromatography process would purify clarified harvest in 43 hours, compared with 75 hours for a batch resin process (Figure 13).

Figure 14 shows that, at the 5000-L production scale, chromatography costs per gram of mAb would reach about €8/g and €9/g for the traditional resin process and full-membrane membrane process, respectively. Productivity is projected to increase from 1.72 g/k€/h for resins to 2.73 g/k€/h for membranes (Figure 15), and the time reduction obtained with a connected membrane process would increase the potential number of production batches per year from 40 to 70.

Conclusion

Our laboratory-scale study and scale-up model show that implementing a full-membrane chromatography workflow for downstream purification of mAbs can be a significant cost-saving alternative to traditional resin-based steps during process development, clinical production, and commercial manufacturing — while meeting requirements for yield, purity, and other product quality attributes. For mature commercial processes, membrane chromatography can address large volumes of antibodies safely using much smaller consumables than are needed for resin-based processing, thus significantly reducing downstream facility footprints: Adopters could perform downstream processing in minimized cleanroom spaces because they would not require columns and packing systems and because they could leverage equipment (such as the Resolute BioSC system) that connects required chromatography and virus-inactivation steps.

Our study also demonstrates that membrane-based processing can achieve CoGs comparable to those for resin-based processes for large-scale and large-demand commercial production based on bioreactor sizes of up to 5000 L. Notably, CoGs for membrane processes can be optimized by reducing buffer consumption for the capture step. Sartorius is optimizing buffer consumption of the Sartobind Rapid A device to help users realize such benefits.

Figure 13: Comparison of chromatography media volumes, cycles, and process times for a resin batch process and a connected membrane process at 5000-L bioreactor scale

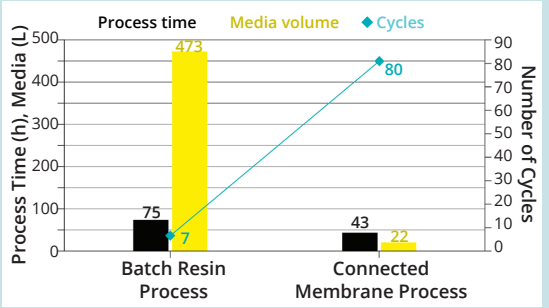


Figure 14: Comparison of total chromatography cost of goods for a resin batch process and a connected membrane process at 5000-L bioreactor scale (40 batches per year), broken down by media, buffers, hardware, labor, and cleaning in place (CIP)

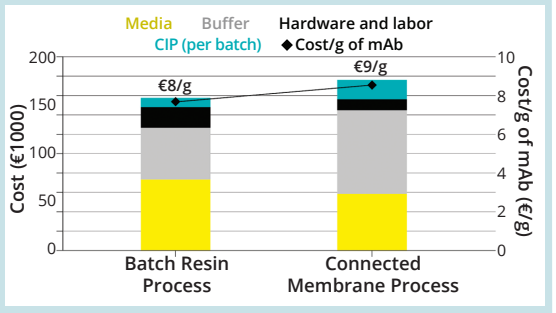
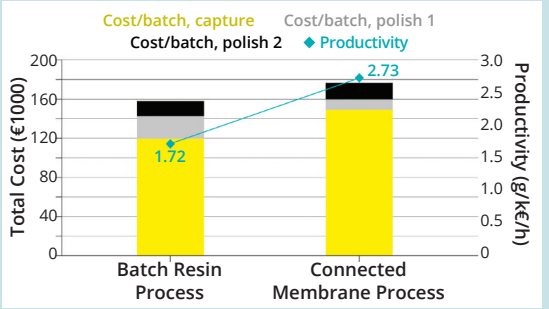


Figure 15: Comparison of total chromatography cost of goods (CoG) broken down by step and productivity level for a resin batch process and a connected membrane process at 5000-L bioreactor scale



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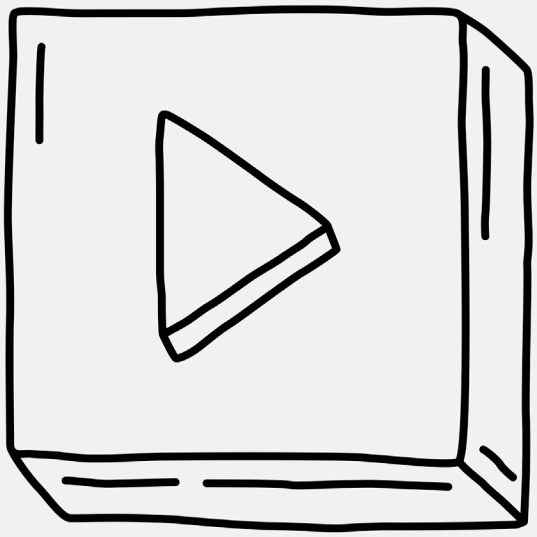

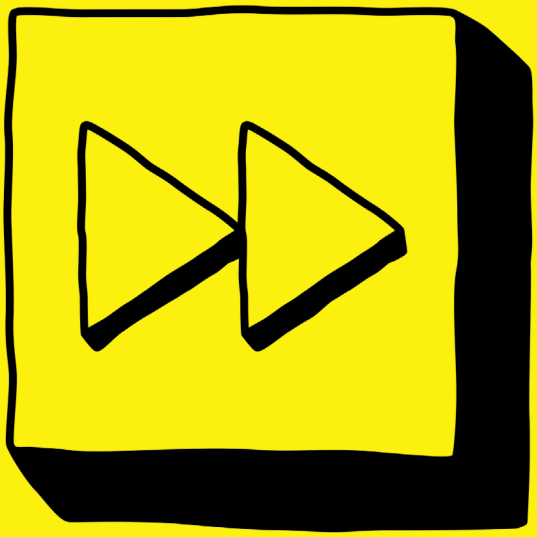

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