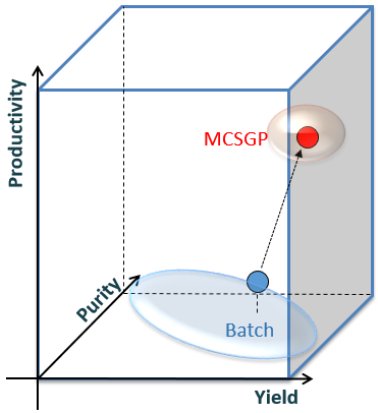
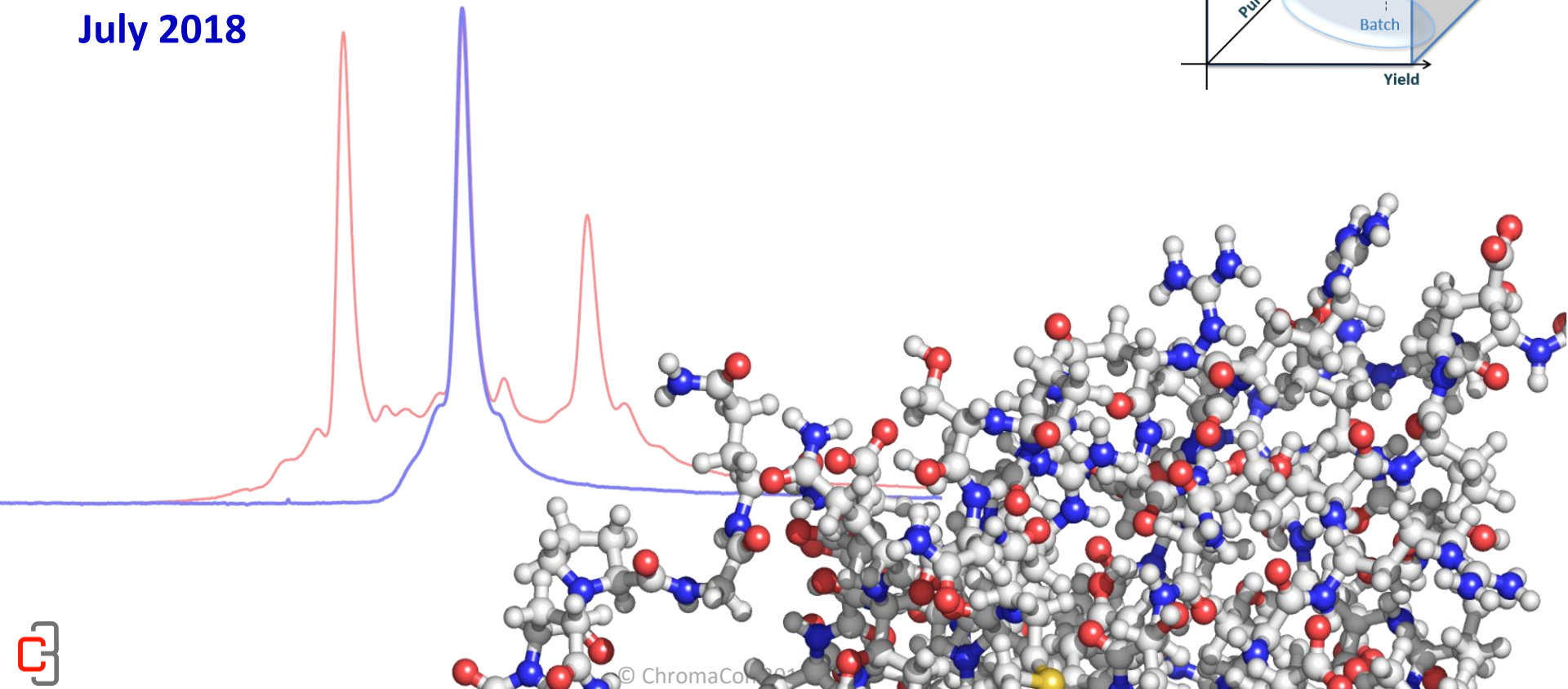
ChromaCon®
A new dimension in purification

Contichrom in Blood Plasma Fractionation



July 2018



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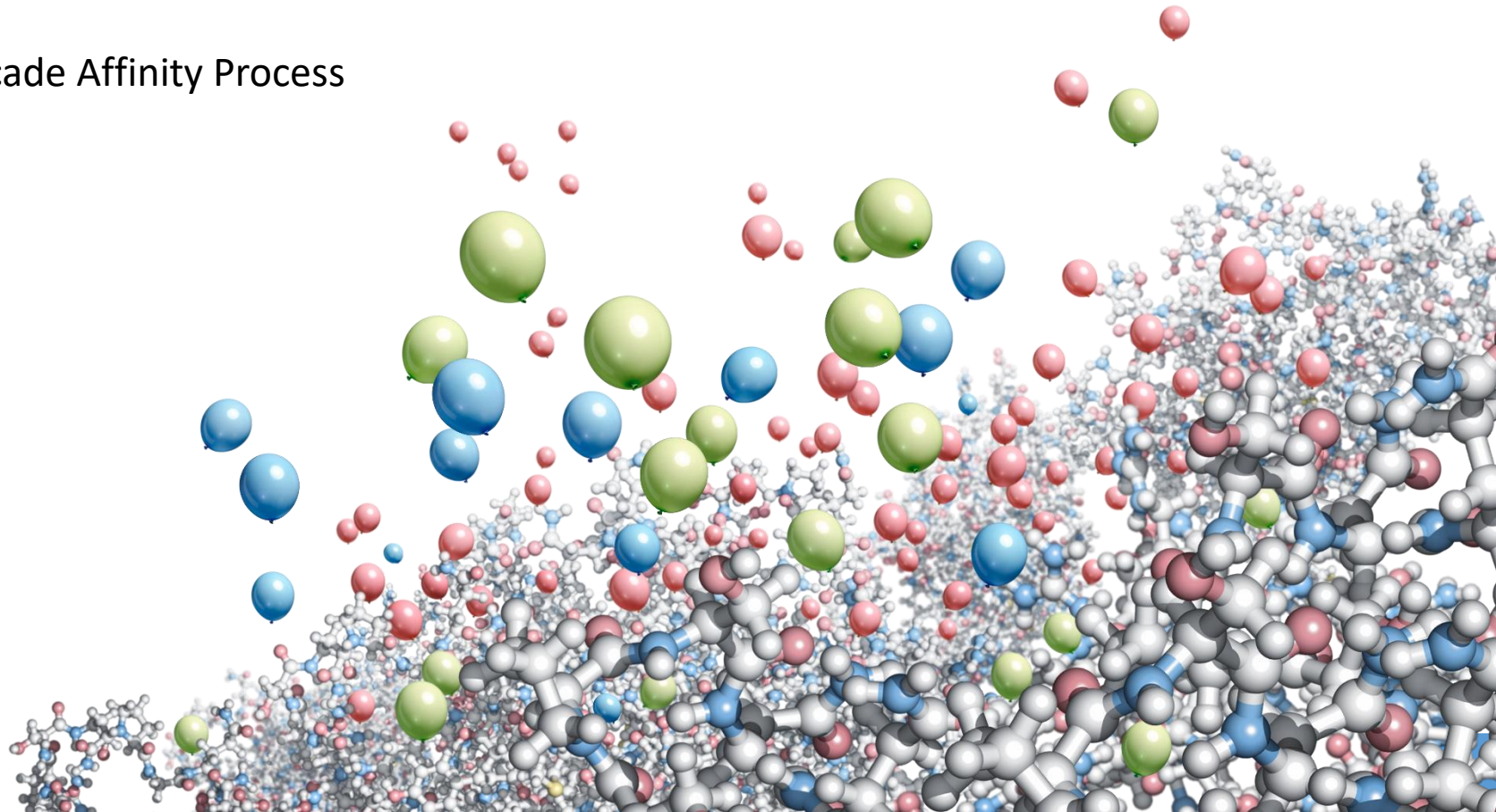
Status Quo

1. Cohn Process
2. Cascade Affinity Process

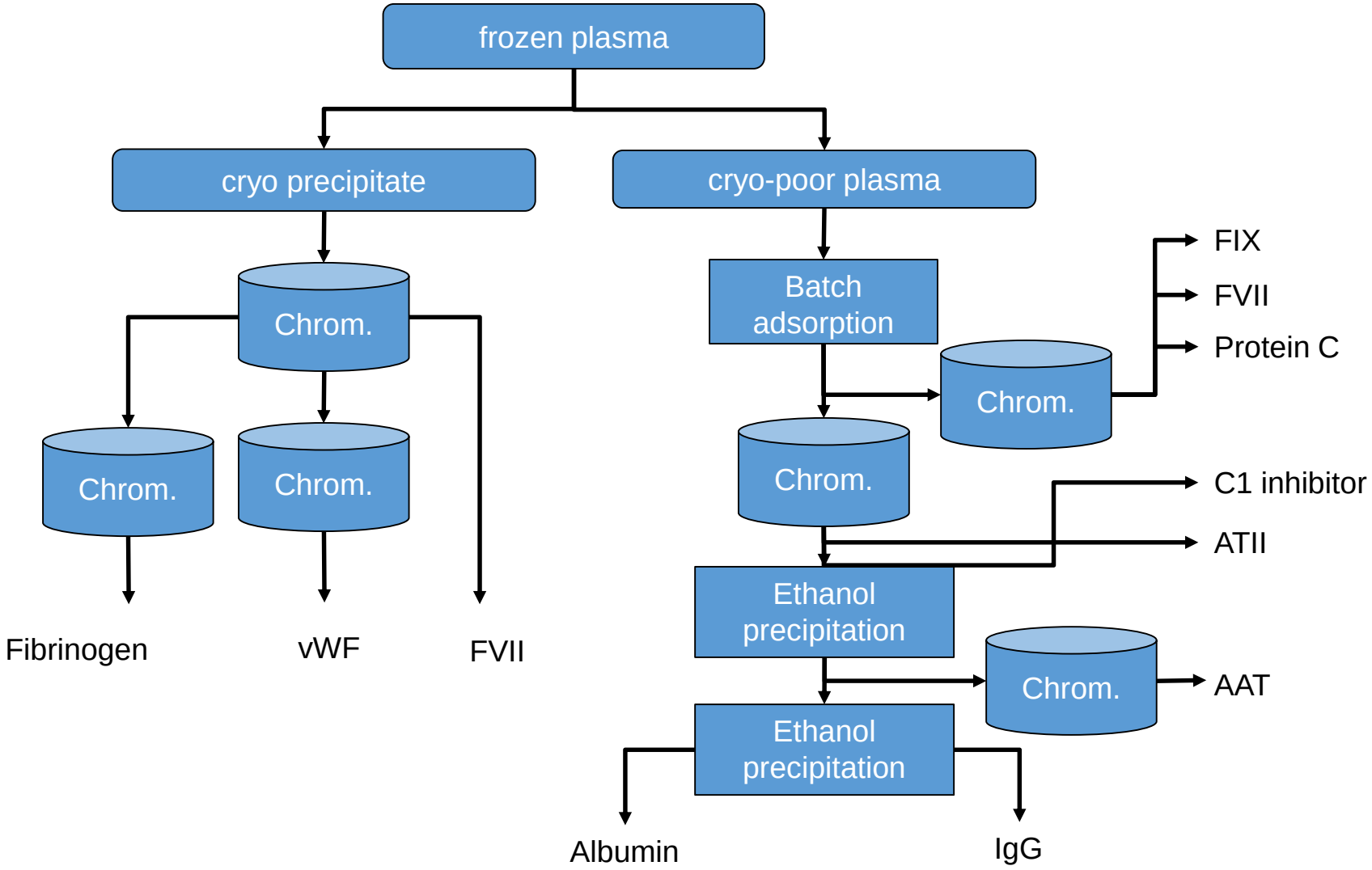


Plasma Fractionation

Today: Most major fractions are generated through non-chromatographic processes:

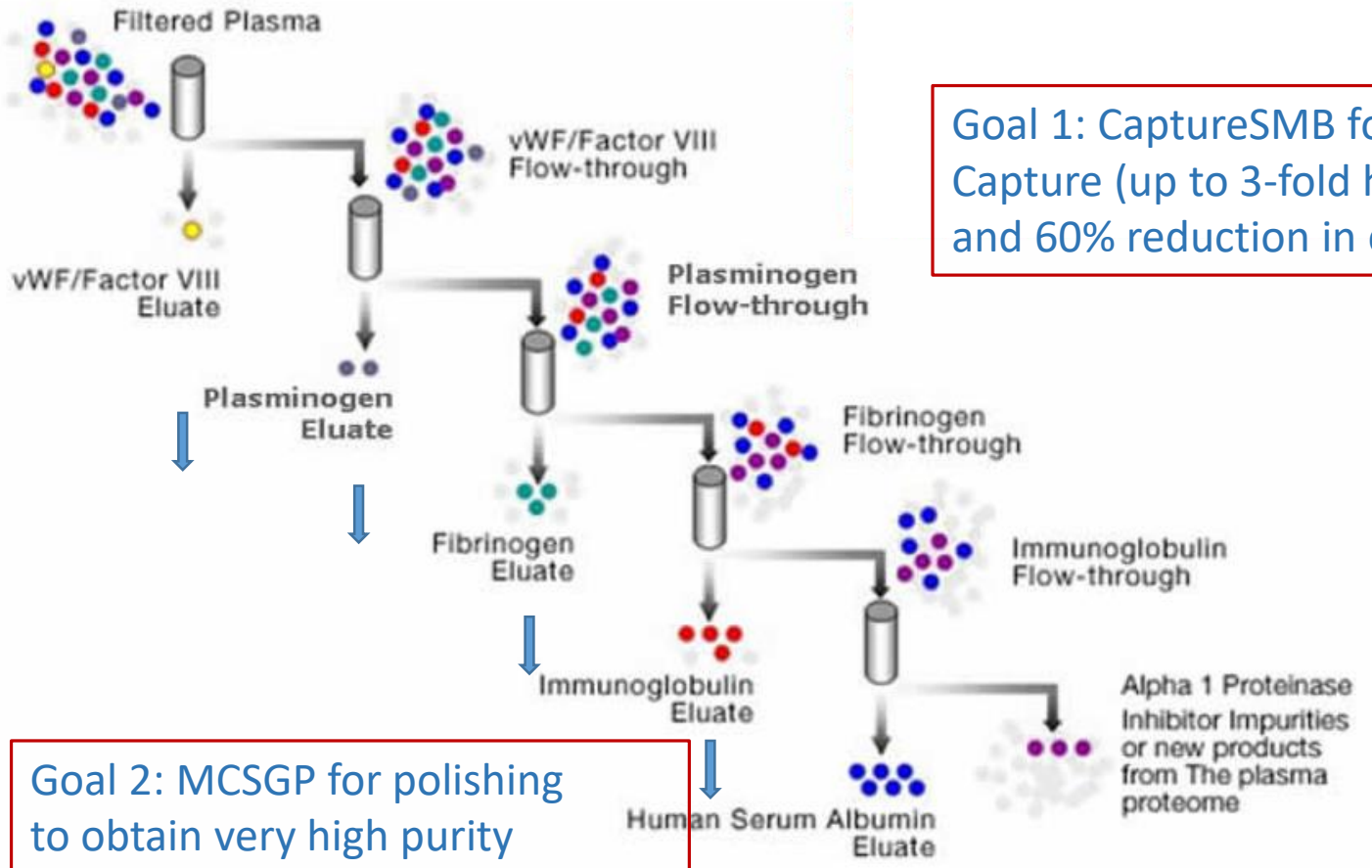
- Cryo-precipitation, Ethanol precipitation
- Side fractions (FVIII, FIX others) are purified by affinity chromatography to obtain purity for clinical use. A few chromatographic steps are on the "critical path“
- Two processes are mostly used: Cohn fractionation with single-column chromatography steps
- Cascade affinity process
- Most affinity resins for plasma products are customized for a product class but not highly specific leading to flat breakthrough curves meaning that you will waste a lot of expensive affinity resins
- Product Yield is very important as plasma supply is limited and safety testing very expensive
- ChromaCon’s technology will increase the yield up to 80% without compromising target purity and will reduce affinity resin costs by up to 60% without changing its use in either the Cascade or the Cohn fractionation process

Status Quo: Cohn Process with Chromatography



Status Quo: Cascade Process (Prometic)

Affinity resin cascade for selective removal of products from plasma feed
Problem: Affinity step not efficient and eluate not pure enough



Goal 1: CaptureSMB for efficient Capture (up to 3-fold higher productivity) and 60% reduction in capture resin cost

Goal 2: MCSGP for polishing to obtain very high purity with up to 80% more yield and 80% less buffer consumption

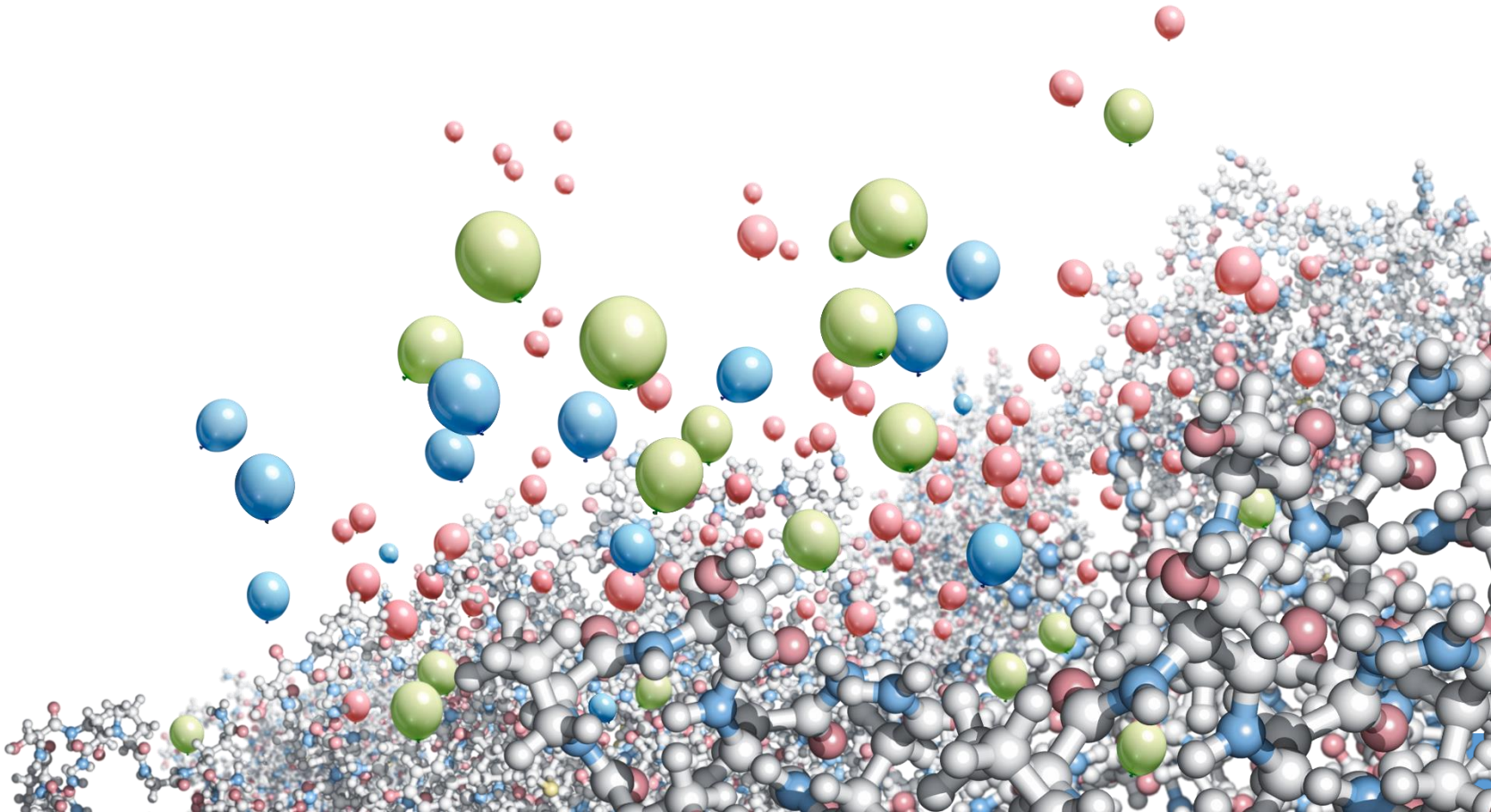
PROMETIC BIOSCIENCES

Purification

A typical purification sequence consist of:

- **A clarification step:** mixed mode, expanded bed adsorption, Monolith…) used to concentrate products from feed stream
- **A capture step:** Affinity, mixed mode, Monolith…)
  high yield and in some cases high purity (affinity) but typically low productivity and expensive affinity matrices (affinity). ChromaCon technology (CaptureSMB) can improve productivity up to 3x and save up to 60% resin
- **A polishing step:** Membrane chromatography. Typically designed as flow-through mode. ChromaCon technology (MCSGP, Flow-2) can improve yield by up to 80% and improve productivity and buffer consumption
- Two virus inactivation steps (virus filtration, pasteurization, UV-C, etc.)
- Prion removal
- Sterile filtration / freeze-drying
- 7 steps each with 95% step yield → 70 % overall yield. ChromaCon technology could improve overall yield to more than 90%

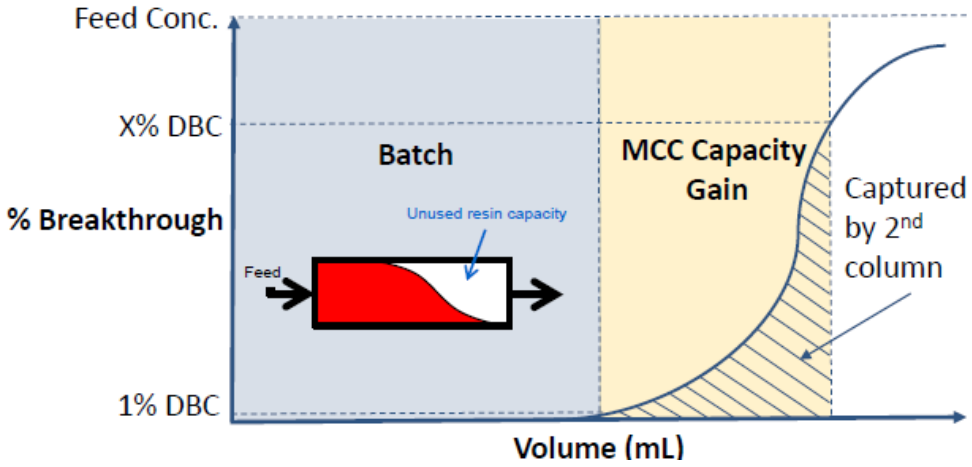
CaptureSMB – a process to maximize affinity capture efficiency



CaptureSMB - A continuous process for affinity capture

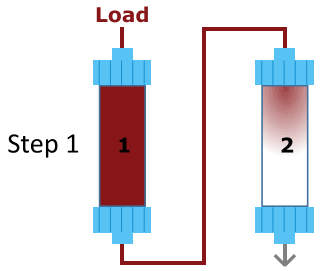
CaptureSMB®: Loading of two interconnected columns to maximize capacity utilization of the first column or to increase throughput.

- Increase Capture step efficiency
- Save up to 60% affinity resin cost
- Process faster and preserve product integrity
- Especially useful if the breakthrough curve is flat (low specificity of affinity resin)

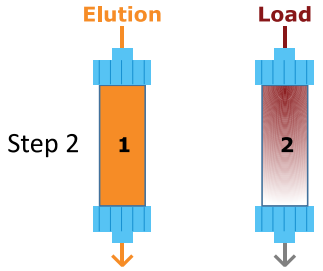


- **In MCC capture, the first column is loaded beyond its 1% DBC**
- **The flowthrough is captured onto the second column in the loading zone**
- **The sequential loading allows for better capacity utilization and productivity without sacrificing yield**

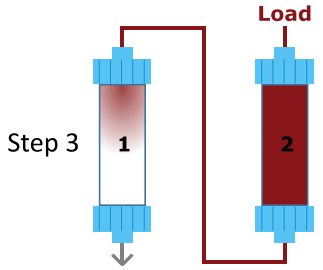
CaptureSMB - A continuous process for affinity capture



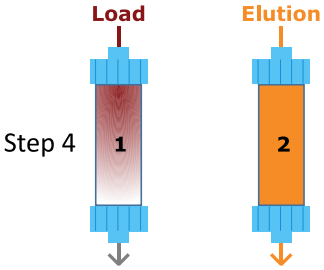
- In the sequential loading phase, columns 1 and 2 are interconnected. Column 1 is fully loaded with sample (red) while its breakthrough is captured on column 2.



- Column 1 is washed, eluted, cleaned and re-equilibrated while loading continues on column 2.

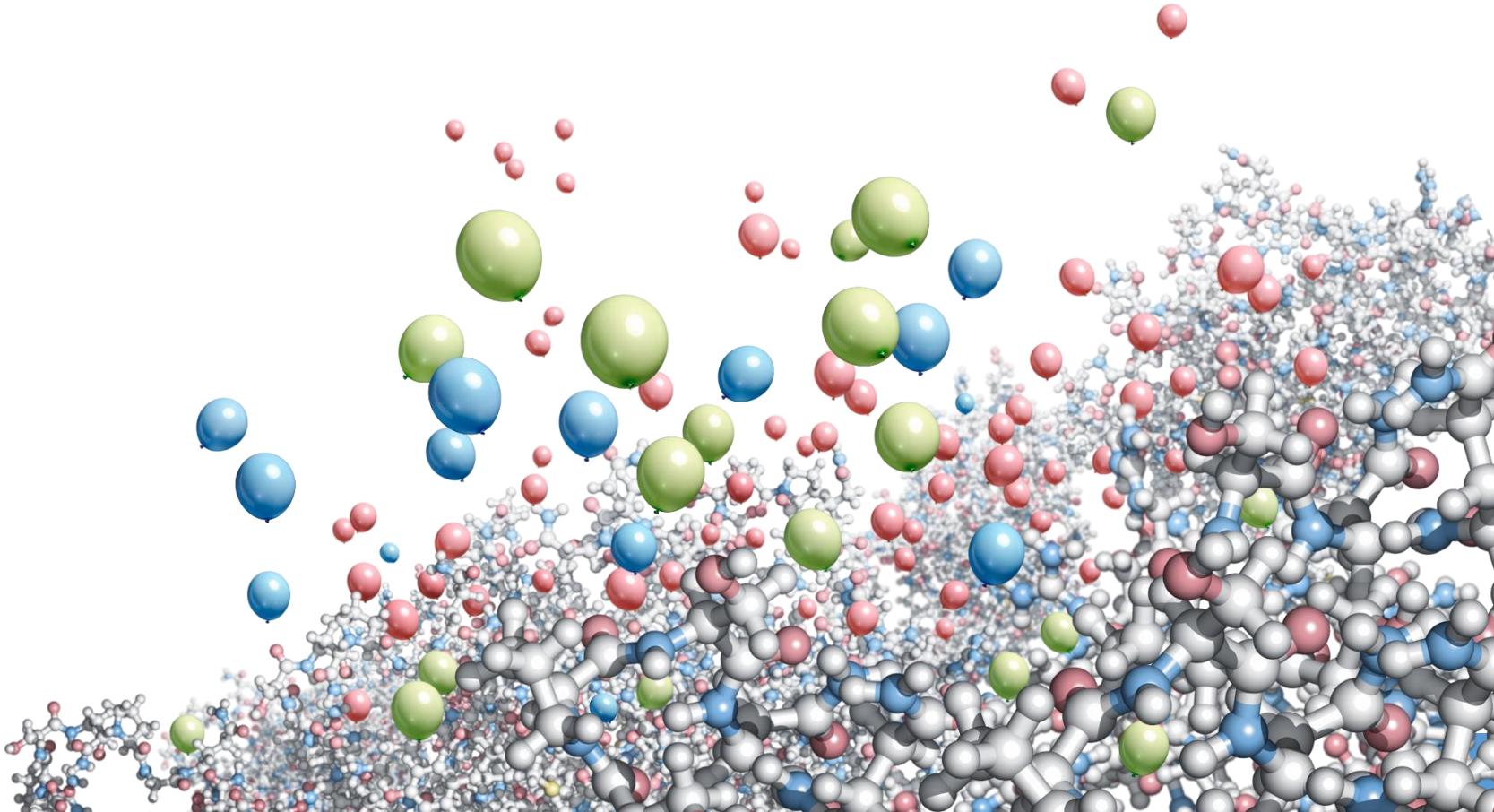


- After regeneration of column 1, the columns are inter-connected and column 2 is fully loaded while its breakthrough is captured on column 1.



- Column 2 is washed, eluted, cleaned and re-equilibrated while loading continues on column 1. This cyclic process is repeated in a continuous way.

MCSGP Process for obtaining higher purity AND yield

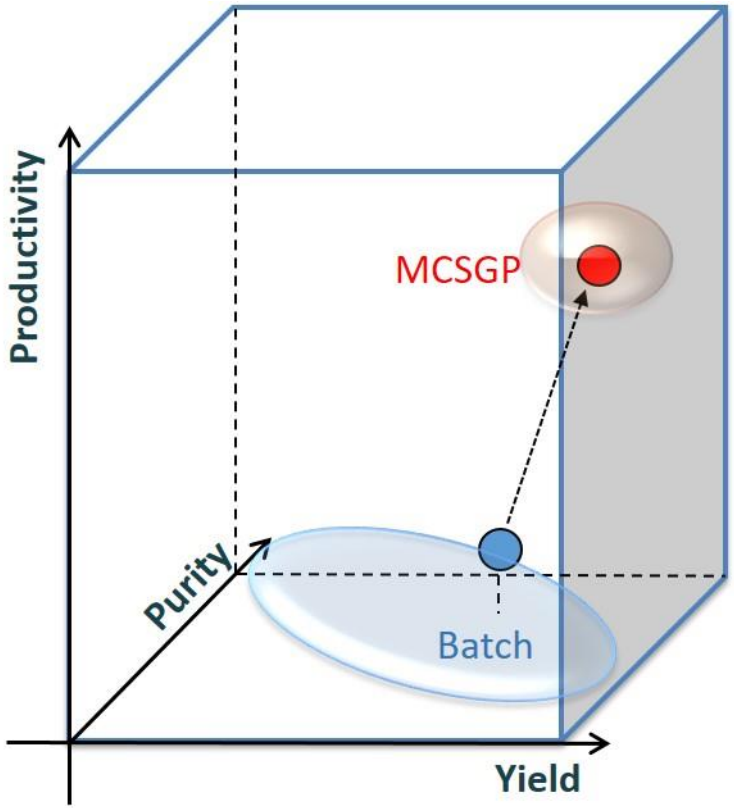


MCSGP Process

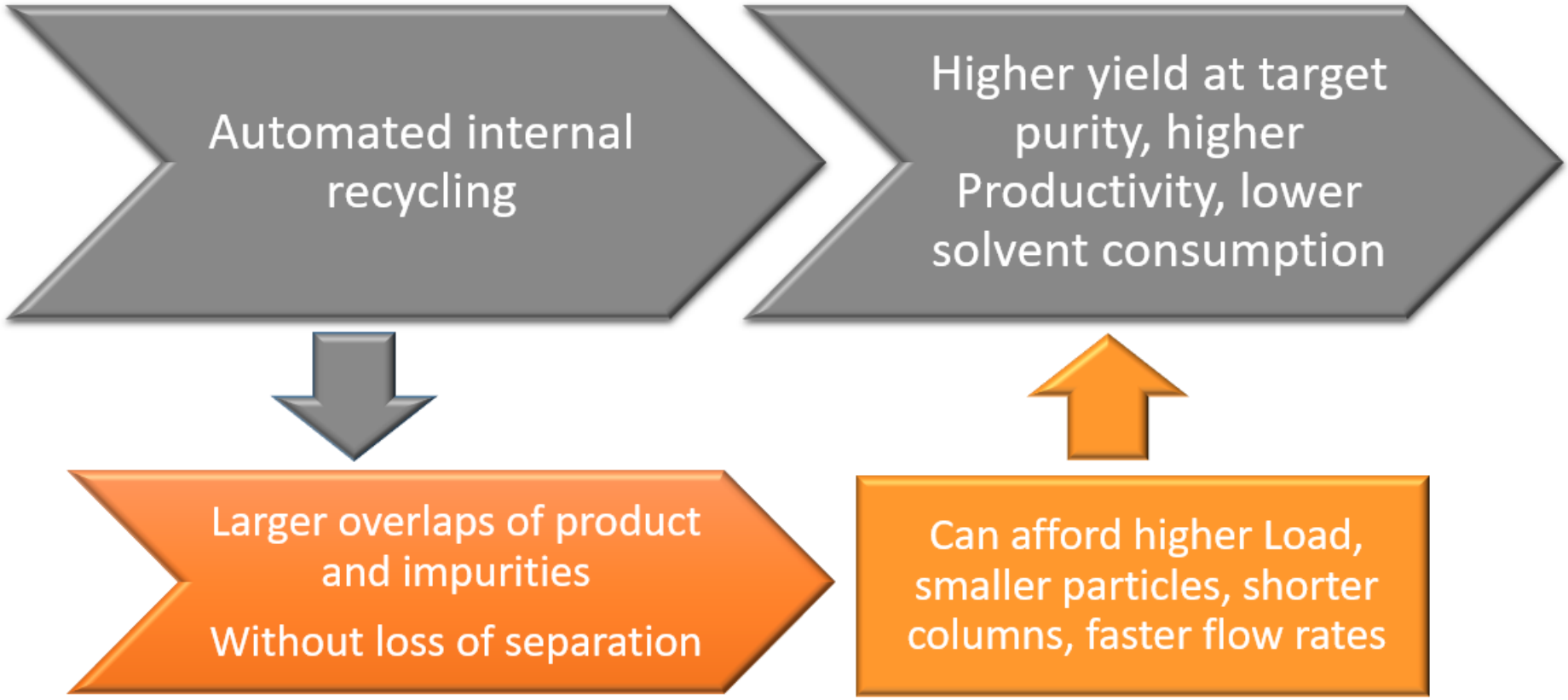
- Batch operates in an essentially 2D continuum between purity and yield with little impact on productivity.
- With MCSGP, both purity AND yield remain high.
- MSCGP also allows up to 10-fold higher productivity and up to 80% reduction in solvent consumption.

The result of this process improvement is:

- Enhanced production capacity (doubling of output)
- Smaller footprint of equipment and utilities
- Lower CAPEX and OPEX
- Lower COG of product
- Better product quality (getting more pure product)

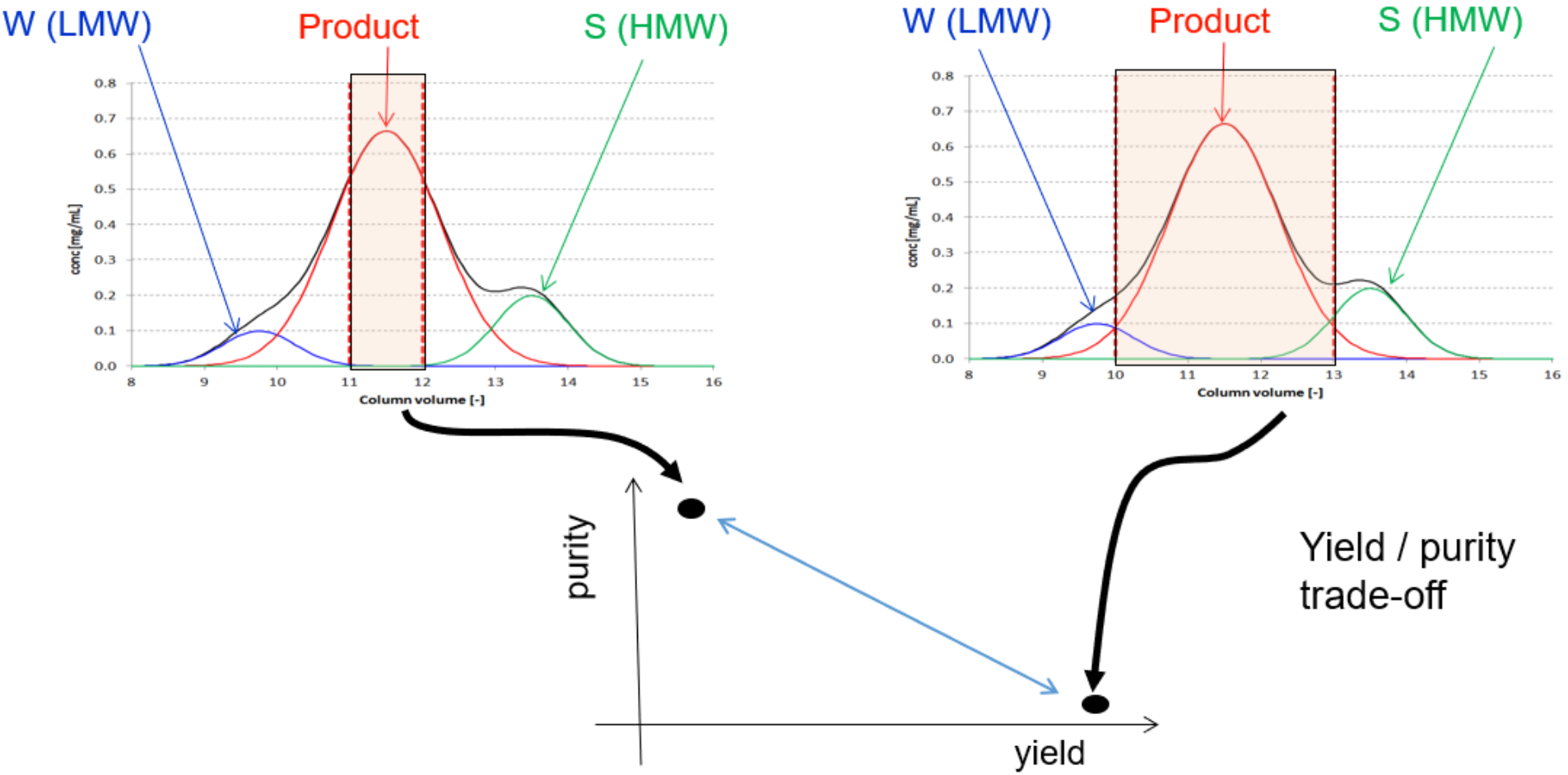


MCSGP advantages compared to single column batch chromatography



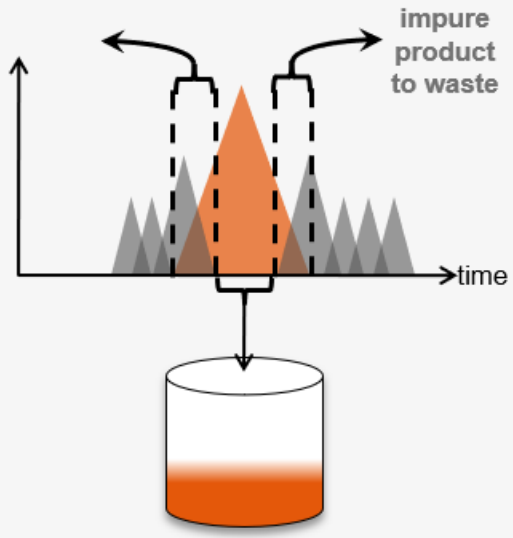
The Single Column Batch Separation Challenge

- Yield-purity trade-off for ternary separations



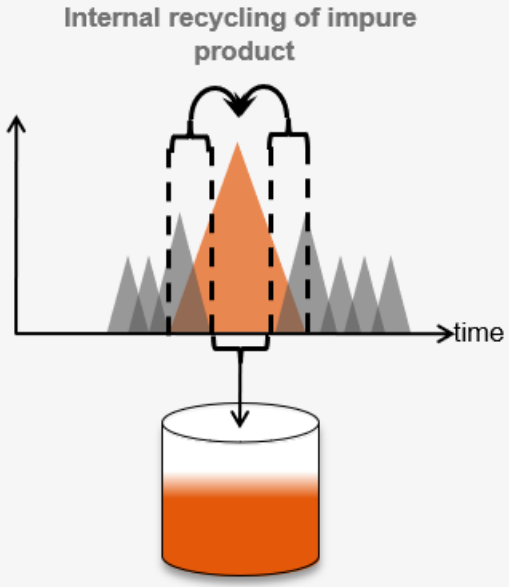
MCSGP principle: recycle until it‘s pure

Conventional single column batch chromatography



pure product

MCSGP chromatography



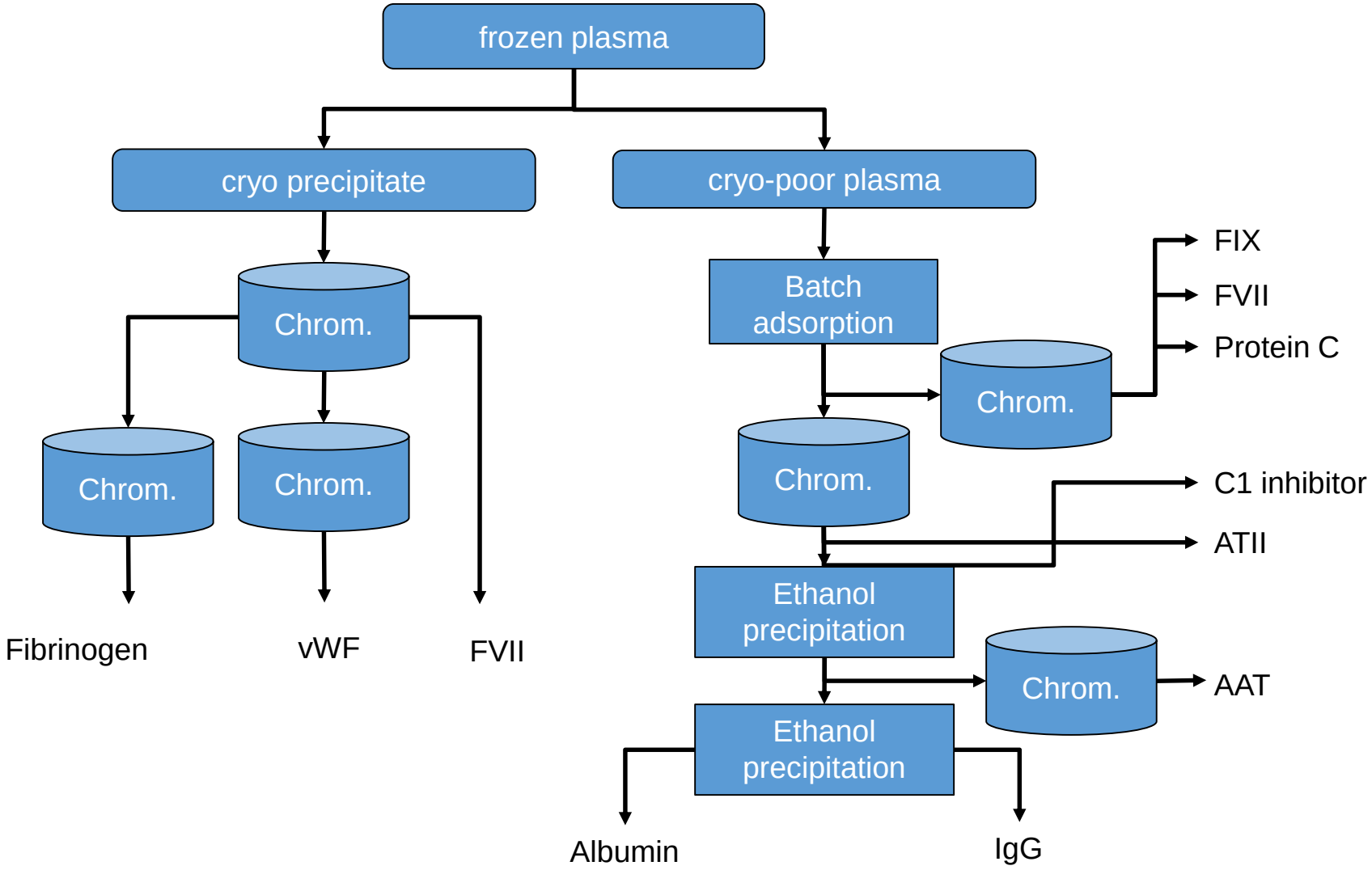
more pure product

MCSGP in Plasma Fractionation

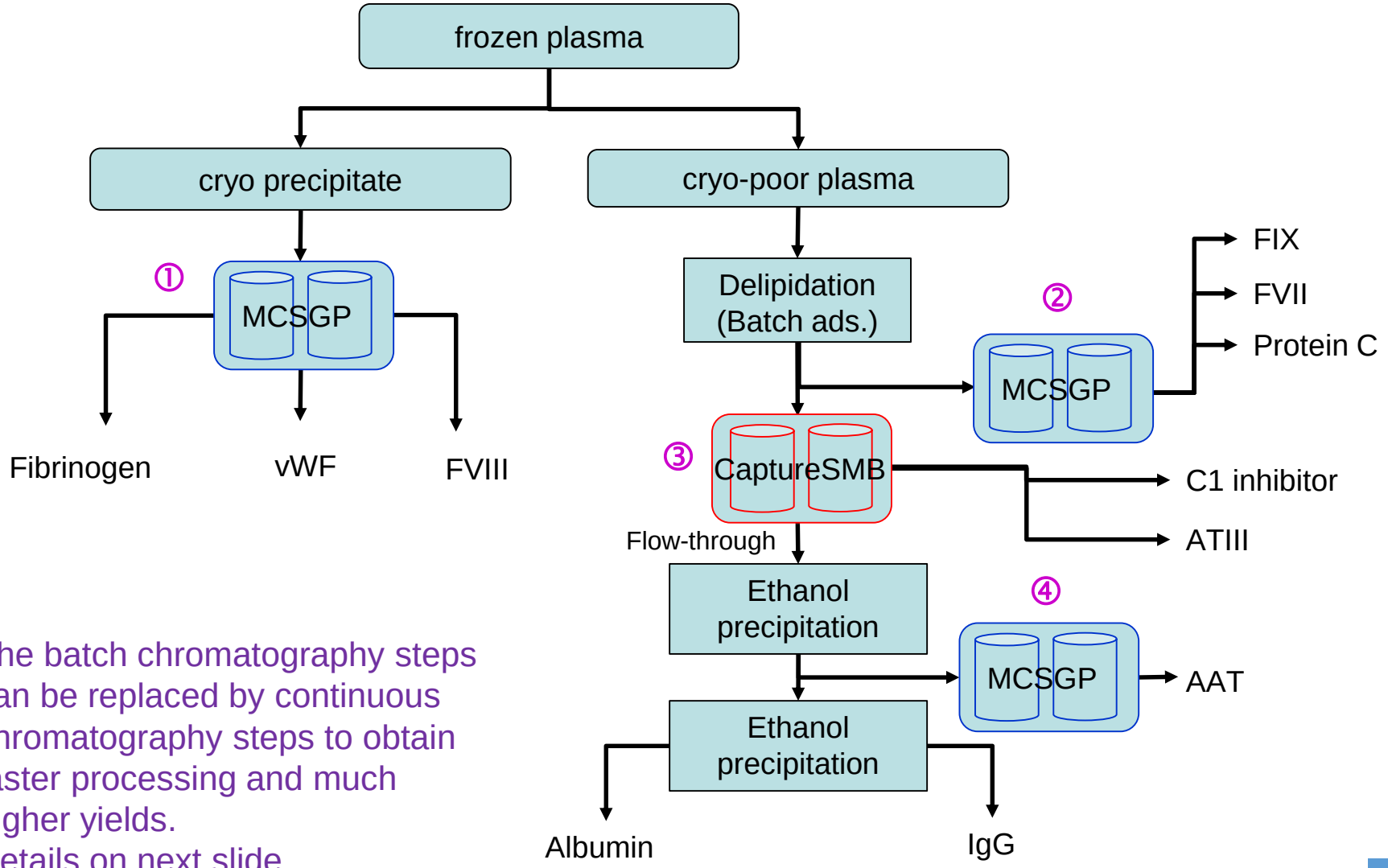
- ChromaCon Technology employing the MCSGP process principle
  - Simplifies the standard plasma fractionation process, resulting in higher yields and lower costs, while retaining the validated virus inactivation steps
  - Provides higher chromatography step yields (up to +80%), leading to more products and lower COG
  - Allows operational cost reduction through buffer and stationary phase savings of up to 60%
  - Reduces CAPEX by 30%

- GMP Process Equipment (LEWA) using and Infrastructure supplied by globally acting partner engineering companies (Glatt)

Plasma Fractionation with standard batch chromatography (Cohn Process with chromatography)



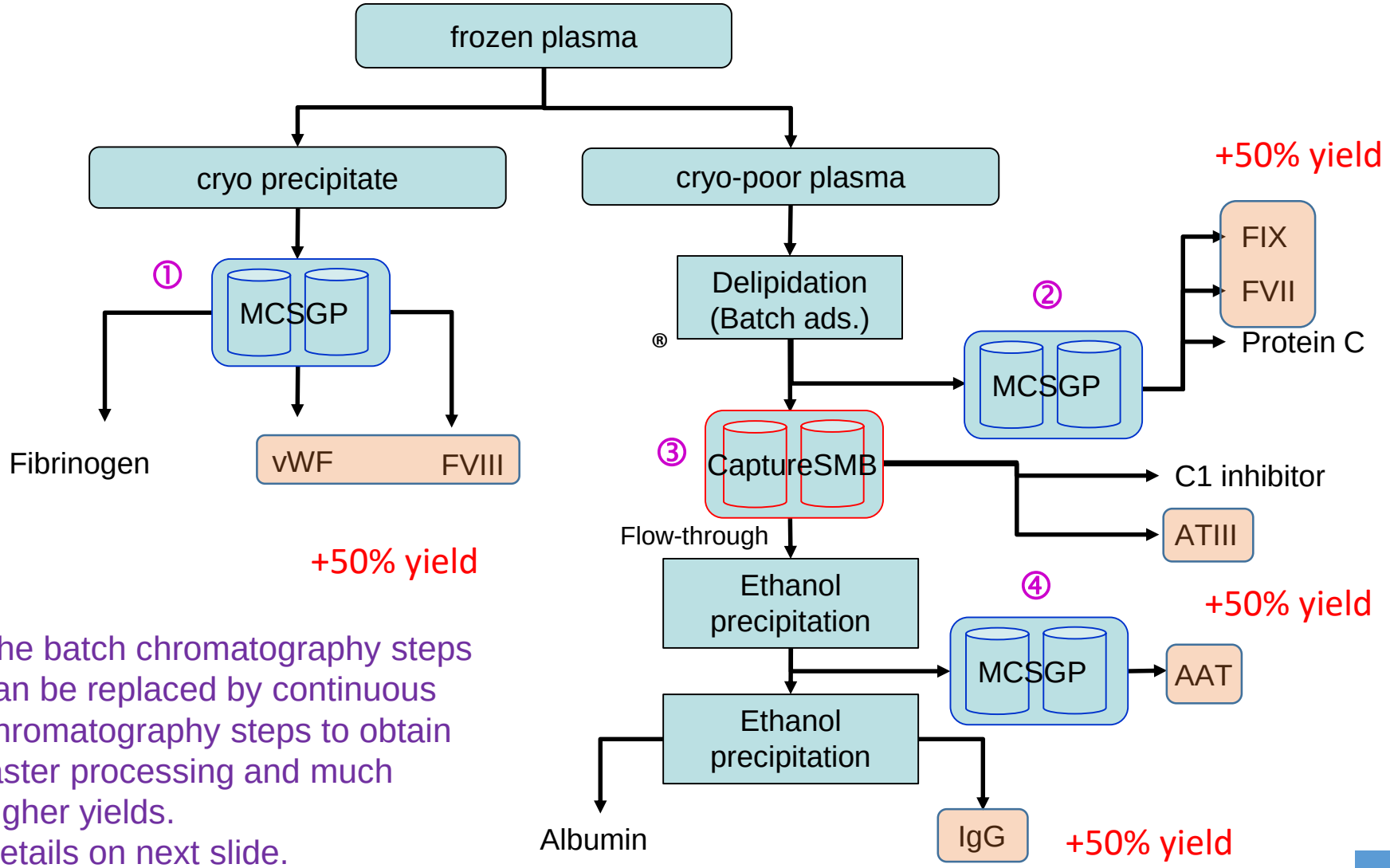
Typical Plasma fractionation process with ChromaCon Technology



The batch chromatography steps can be replaced by continuous chromatography steps to obtain faster processing and much higher yields.
Details on next slide.

ChromaCon Technology for Plasma Fractionation

Modified Cohn Process to optimize yield for high value plasma proteins



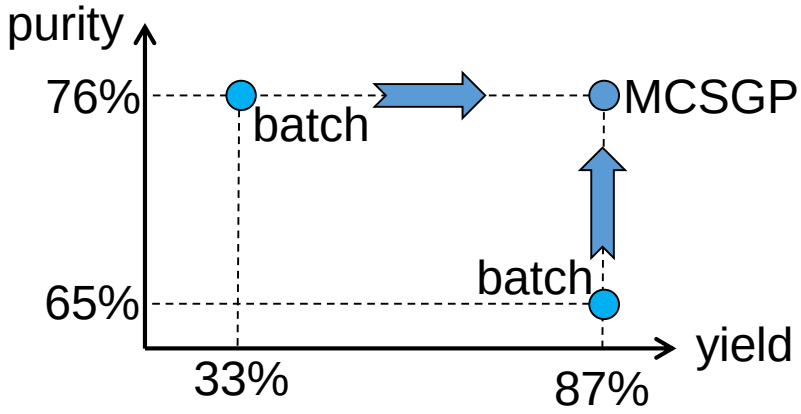
The batch chromatography steps can be replaced by continuous chromatography steps to obtain faster processing and much higher yields.
Details on next slide.

Typical Plasma fractionation process with Contichrom

- Application ① (cryo-precipitate branch) A Contichrom® unit (MCSGP) is used to obtain high-purity Factor VIII and optionally fibrinogen and vWF. Expected Factor VIII yield increase: at least 50%.
- Application ② (cryo-poor plasma branch): Contichrom® unit (MCSGP) is used to isolate Factor IX with high yield and purity. Expected Factor FIX yield increase: at least 50%. In this step, there is the option to isolate FVII and Protein C.
- Application ③ (cryo-poor plasma branch): A Contichrom® unit (running the CaptureSMB® process) is used to isolate AT-III by Heparin affinity chromatography. The flow-through is processed further for purification of IVIGs and Albumin using the traditional pathway.
- Application ④ (cryo-poor plasma branch): A Contichrom® unit (MCSGP) is used to purity Antitrypsin (AAT) with high yield and purity.
- If the IgGs need to be purified to high purity IVIGs, the Contichrom® unit can be also used for this task

Typical Plasma fractionation process with Contichrom

- Application ④ (cryo-poor plasma branch): A Contichrom® prep unit (MCSGP) is used to purify Anti-trypsin (AAT) with higher yield and purity when compared to batch chromatography:



(results presented at SPICA 2012 conference by ETH Zurich, slides available through ChromaCon)

- Application ③ (cryo-poor plasma branch): Isolation of AT-III by Heparin affinity chromatography using the CaptureSMB® process. (see case study below)

Typical Plasma fractionation process with Contichrom

- Potential improvement of Cohn process: By using chromatography
  → increasing yield of AAT (=A1PI), the revenues can be increased significantly

- With Contichrom a further 50% improvement is possible
  → >1'000 USD/L plasma

Cascade	vWF/FVIII	IgG	Albumin	A1PI	
Yield	52%	70%	73%	68%	
$/g	$10,000	$38	$2.25	$330	
g/batch	18	20,975	89,500	3,552	
$MM / yr	26.7	117.2	29.6	172.3	
$ / L plasma	$52	$228	$57.5	$335	**$672.5**

Cohn	vWF/FVIII	IgG	Albumin	A1PI	
Yield	18%	51%	86%	15%	
$/g	$10,000	$38	$2.25	$330	
g/batch	6	15,243	105,000	798	
$MM / yr	9.1	85.1	34.7	38.7	
$ / L plasma	$18	$165.5	$67.5	$75	**$326**

Batch size = 3,500 litres

Source
A comparative study of Cohn and chromatographic fractionation using a novel affinity "Cascade Process".
John Curling, Dev Baines, Christopher Bryant, Ruben Carbonell, Tom Chen, Patrick Gurgel, Timothy Hayes
4th Plasma Product Biotechnology Meeting
Porto Elounda, Crete, Greece, 9-12 May 2005

MCSGP Process Calculations

- Cryo-poor plasma (3‘500 kg purified product p.a.)

Performance overview			
		batch	**MCSGP**
Productivity (throughput)	[g/L/hr]	**0.9**	**3.4**
Buffer consumption	[L/g]	**3**	**1.2**
Buffer consumption per month runtime	[m3/month]	**863**	**345**
Overall volume of stationary phase	[L]	**331.8**	**142.5**
Units dimensions (no limit on column i.d.)			
Number of columns per unit	[-]	**1**	**4**
bed height	[cm]	**25**	**15**
column inner diameter	[cm]	**130**	**55**

- Conclusion: due to high-volume throughput, MCSGP seems to be the only feasible option

Estimated unit dimensions (cryo-precipitate)

- Cryo-precipitate (100 kg purified product p.a.) :

Performance overview			
		batch	**MCSGP**
Productivity (throughput)	[g/L/hr]	**1.0**	**4.1**
Buffer consumption	[L/g]	**5**	**2**
Buffer consumption per month runtime	[m3/month]	**38**	**15**
Overall volume of stationary phase	[L]	**12.3**	**3.5**
Units dimensions (no limit on column i.d.)			
Number of columns per unit	[-]	**1**	**3**
bed height	[cm]	**25**	**15**
column inner diameter	[cm]	**25**	**10**

- Conclusion: MCSGP provides higher product yields and lower operating costs

OPEX savings with MCSGP Process

- E.g. for cryo-poor plasma

		batch	MCSGP	OPEX reduction by MCSGP
Buffer consumption per month runtime	[m3/month]	863	345	-60
Overall volume of stationary phase	[L]	331.8	142.5	-57

- Assuming 0.2 €/L buffer (WFI quality), 1L stationary phase 1‘000 € and 1 year lifetime of stationary phase
- Estimated annual buffer & resin cost:
  batch=2‘400 k€, MCSGP=970 k€
- **Annual buffer/resins savings: 1‘430 k€**
- Estimated additional cost savings of 0.5 M€ due to lower labor and maintenance cost
- **Annual total savings: up to 2 M€**

CAPEX Savings with MCSGP (Greenfield)

- Due to significantly smaller footprint and utility use, estimated reduction in CAPEX is up to 30%
  (10 M€ for a total budget of 100 M€)

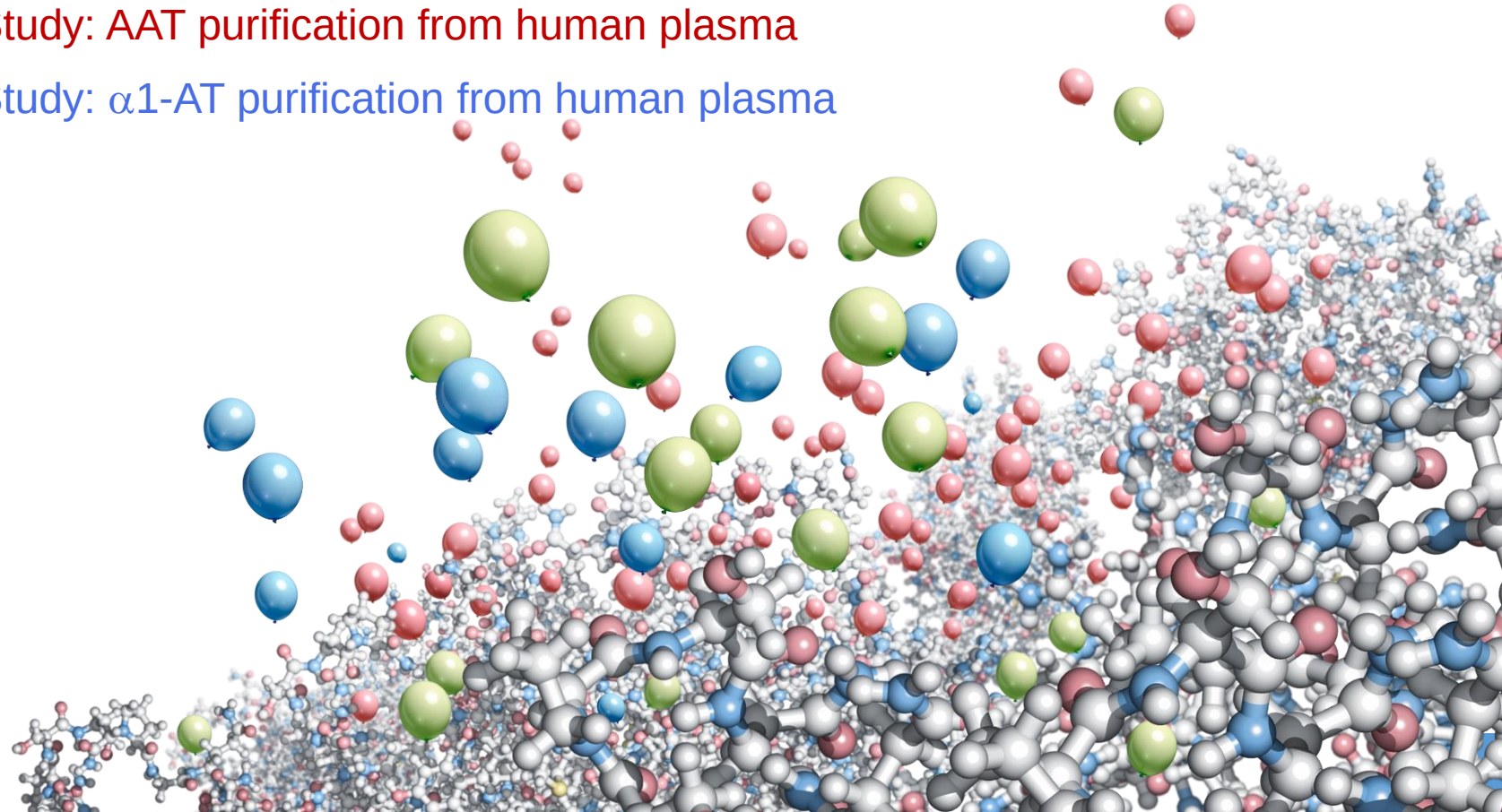
- Detailed unit dimensions and subsequent CAPEX reduction estimate need to be refined in basic engineering phase

Case Studies: Contichrom® for Plasma Fractionation

Modified Cohn Process using CaptureSMB and MCSGP to optimize yield and purity for high value plasma proteins

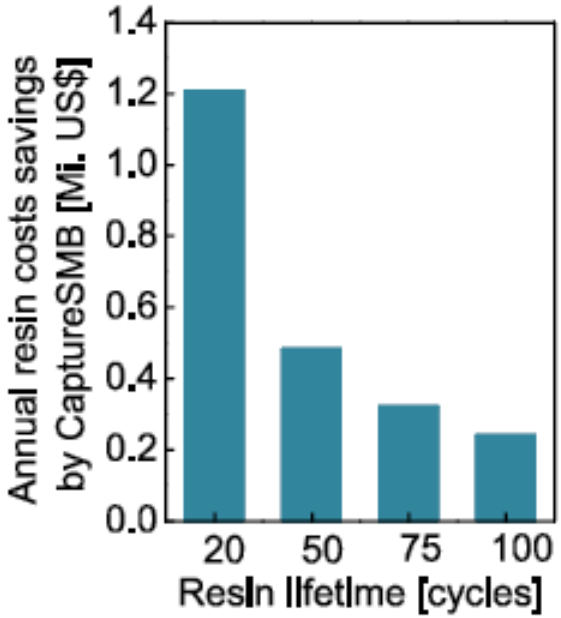
Case Study: AAT purification from human plasma

Case Study: α1-AT purification from human plasma



Case study: α1-AT purification from human plasma

- Capture of AT-III from pre-treated plasma using heparin affinity chromatography
- Superior performance of CaptureSMB in comparison to batch chromatography:
  - 45% higher loading
  - 38% higher productivity and 29% reduction in buffer consumption



Plasma processed per year	[L]	492800
Pool size	[L]	1600
Pool processing time	[h]	24
AT III concentration	[g/L]	0.1
AT III amount per pool	[kg]	0.16
Effective production per year	[Kg]	49.28
Heparin affinity resin costs	[US$/L]	8200*

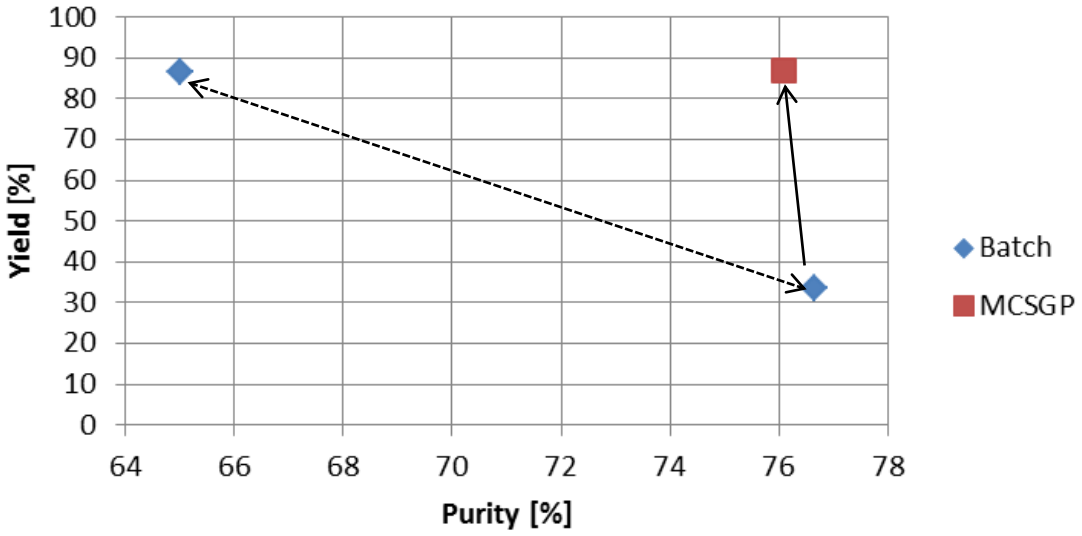
Materials and Methods

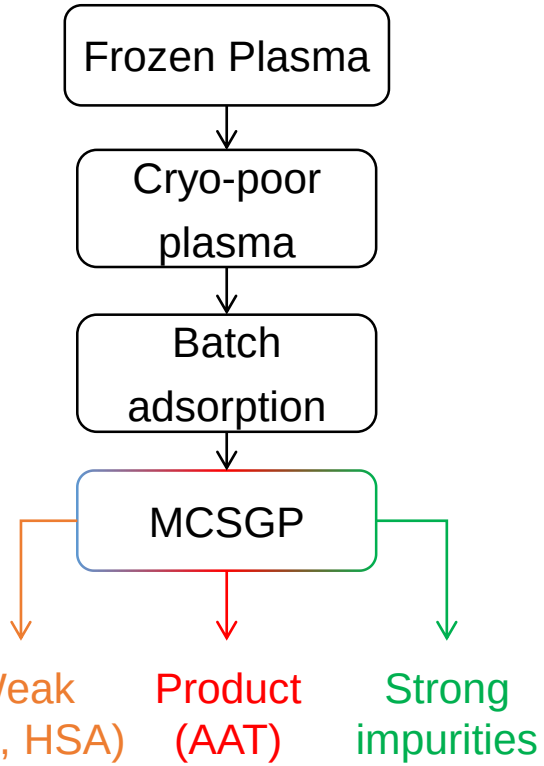
- Feed: cryo-supernatant from human plasma (AT III: 0.08-0.24 g/L)
- Column dimensions: Batch (ID 0.5cm x BH 10cm)
  CaptureSMB (ID 0.5cm x BH 5cm).
- Resin: Toyopearl® AF-Heparin HC-650 M (Tosoh bioscience)
- Analytics: TSKgel Heparin-5PW (Tosoh bioscience)
- Chromatographic equipment: ContiChrom® Lab-10 (ChromaCon AG)

Monica Angarita et al. Poster presentation SPICA 2014

Case study: α1-AT purification from human plasma

Replacement of a batch DEAE chromatography step by MCSGP chromatography (same resin)



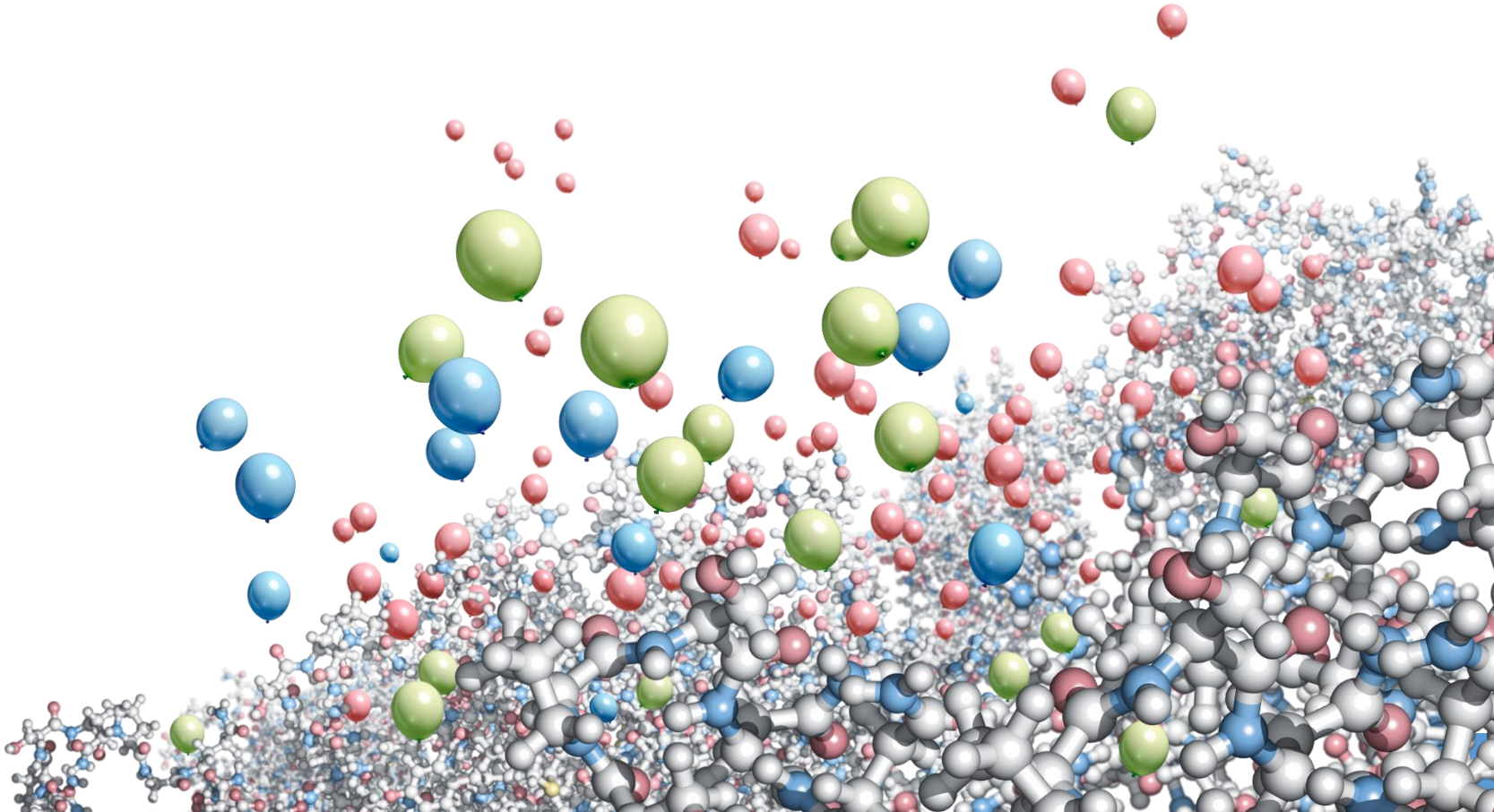


ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

D CHAB
Department of Chemistry and Applied Biosciences

	Purity [%]	Yield [%]
Batch (max. P)	76.7	33.4
Batch (max. Y)	65.0	86.5
MCSGP	**76.1**	**86.7**

Equipment



Process Development Equipment: Contichrom

The Contichrom® CUBE / Combined System

Specifications:
CUBE 30: 0.1-36 mL/min
CUBE 100: 0.1-100 mL/min
UV-LED detectors at 280 & 300 nm,
optional 260 nm
optional external detector 190-500nm
Pressure rating:
50 bar (FPLC)
100 bar (HPLC)

Optional external
Multiwavelength detector
190-700 nm

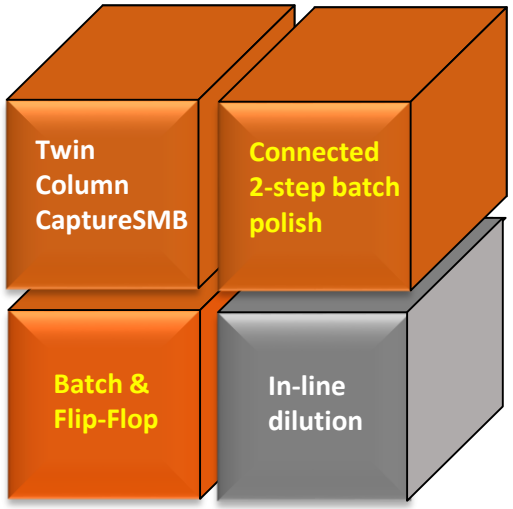
EcoPrime Twin® GMP system for CaptureSMB

Multi-Function System with several process choices

Hybrid System for Stainless Steel connected to disposables USP/DSP

Implemented at pilot/process scale with reference customer (BMS)

Aspen Award 2017 for excellence in Bioprocessing



Risk reduction, process intensification with small equipment footprint and manufacturing flexibility

EcoPrime Twin® MCSGP Scale-up: FPLC and HPLC Systems

Select features*

- Ability to run batch and MCSGP
- Platform design
- Integrated Buffer In-line Dilution
- Scale-up method conversion from CUBE to EcoPrime methods
- Allan-Bradley Rockwell and DeltaV operating systems
- Enables compliance with 21CFR part 11, and others
- Alarm and event logs, access control
- Drain & blow dry
- CIP & and aseptic single use connectivity (LPLC)
- Cleanability of all wetted parts
- Flow accuracy: 0.5% - 1.0% variation.
- Gradient accuracy: 0.5% - 1.0% variation
- Pressure rating: 7.5 bar (up to 100 bar for ATEX non-GMP MCSGP units)
- Flow path: stainless steel
- Equipment payback time of < 1year

Example of MCSGP LPLC system ranges*

Type	Min L/min	Max L/min
Ecoprime 100	0.004	0.6
Ecoprime 250	0.02	3.0
Ecoprime 500	0.06	10

Example of MCSGP HPLC system ranges*

EcoPrime Twin HPLC	Flow rate range* [L/h]		Column ID range [cm]		Linear velocity range [cm/h]	
100	0.5	40	5	10	25	509
250	2	200	10	20	25	637
500	7.5	500	20	45	24	314
1000	17.5	1000	30	60	25	354

* Low and High Pressure MCSGP Twin models may vary in features noted

Moving fast with twin-processes

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