

Journée du Club d'Expertise Chimique de Méditerranée
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La Chromatographie Industrielle Basse Pression Réalités et Perspectives

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www.novasep.com



Content



About Novasep

What we offer

Novasep's technology portfolio:

Chromatography

Ion Exchange

Membrane
filtration

Electrodialysis



About Novasep

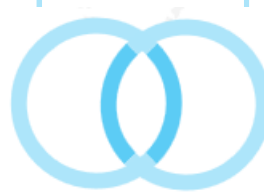
What we do

We deliver **services** for
the **Life Science industries**
with **specialized & differentiating technologies**



2 services

Development and
contract manufacturing
of active ingredients



Process engineering and
supply of purification
equipment

Novasep Group

Services and technologies
for life science and chemical industries



Industrial Biotech
Synthesis
Biopharma

Organized in 3
Business Units

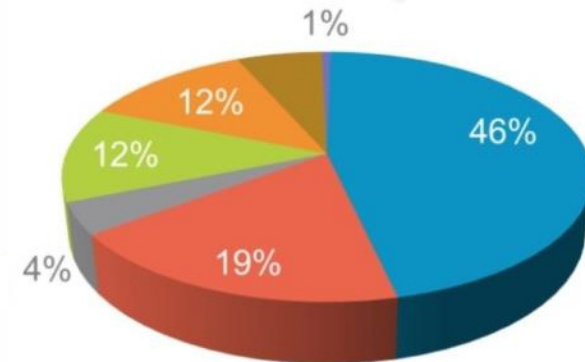
passion & smart processes



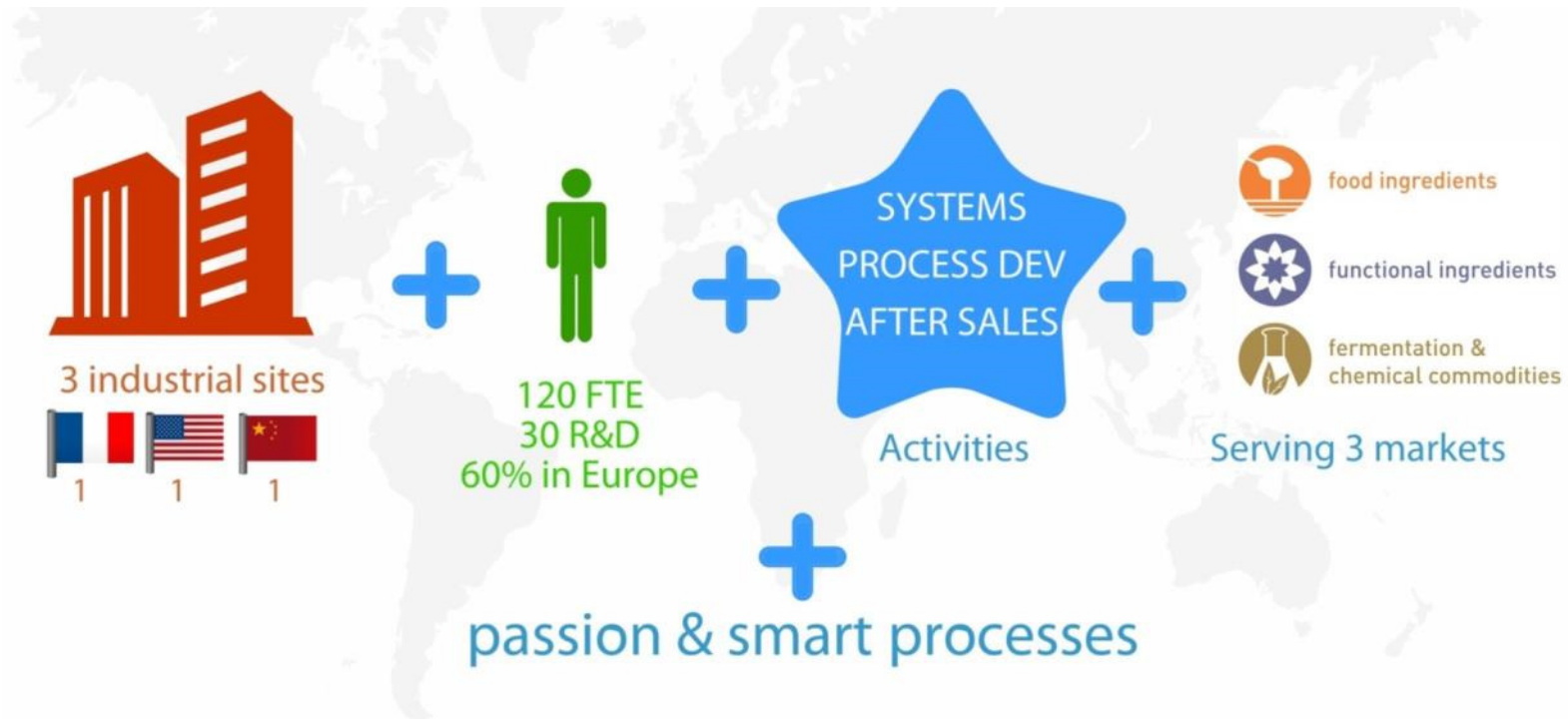
2015
€267m SALES
4% R&D/Sales

- pharmaceuticals
- biopharmaceuticals
- fine chemicals
- agrochemicals
- food ingredients
- functional ingredients
- fermentation & chemical commodities

Serving 7 markets



Industrial Biotech BU at a glance



Industrial Biotech BU Worldwide



Boothwyn PA - USA

Process Development
Pilot
Sales office



S.-M.-de-Beynost - FR

Process development
Pilot, Engineering

Stavropol - RU

Sales office



Shanghai - CN

Process Development
Pilot, Engineering

Bangalore - IN

Sales office

Bangkok - TH

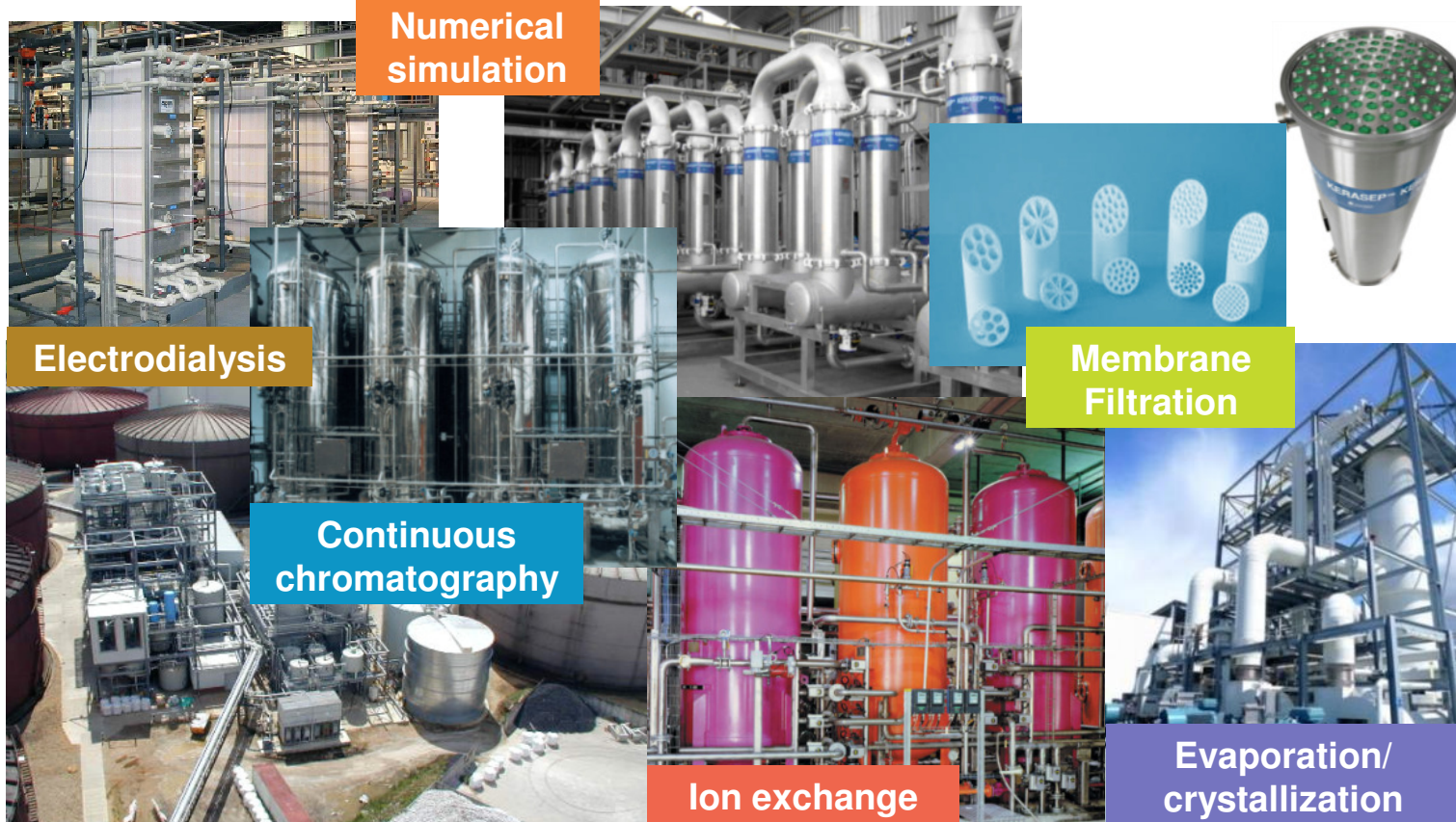
Sales office
Process development



What we offer

Novasep's Technology Portfolio

A wide range of technologies

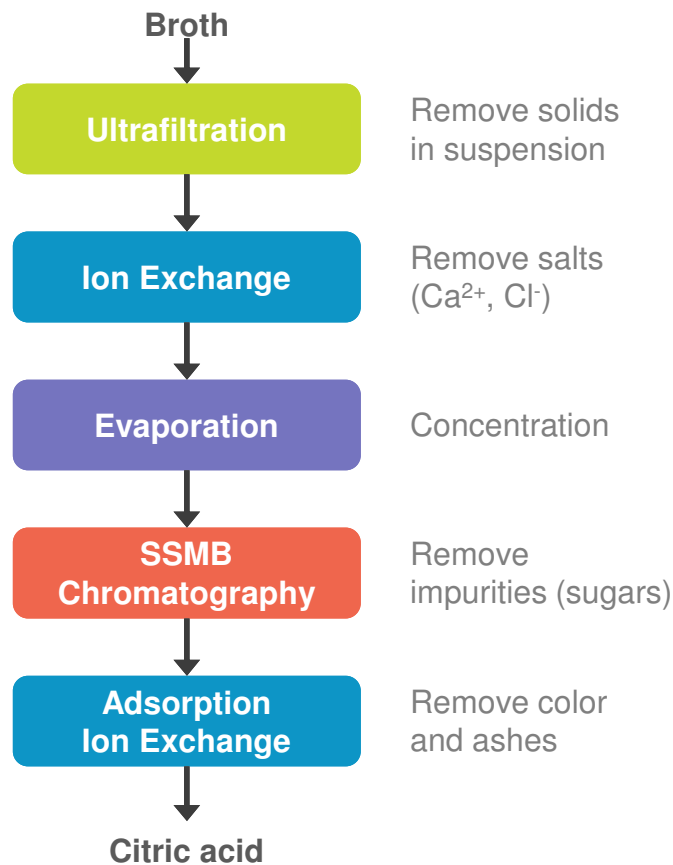


Marketed products prices typically **< 2€/kg**
From **5 – 250 kT/year**

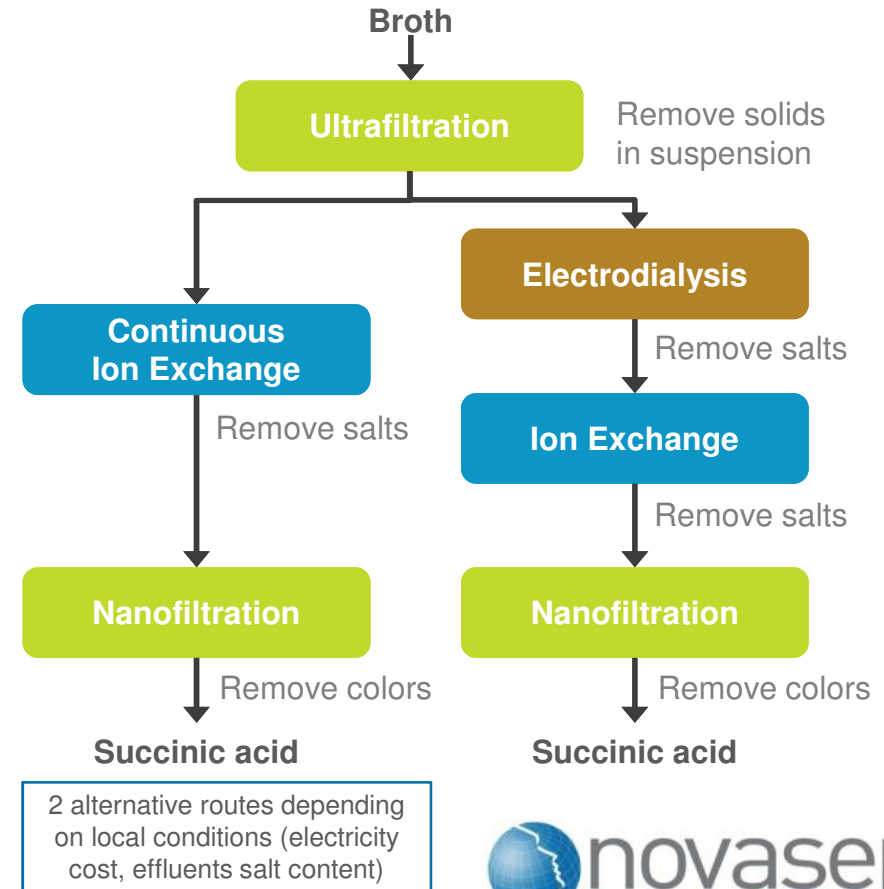
Combining technologies

Novasep's strength: combining technologies to fit your requirements
(cost, performances, purity levels, yield, local conditions, ...)

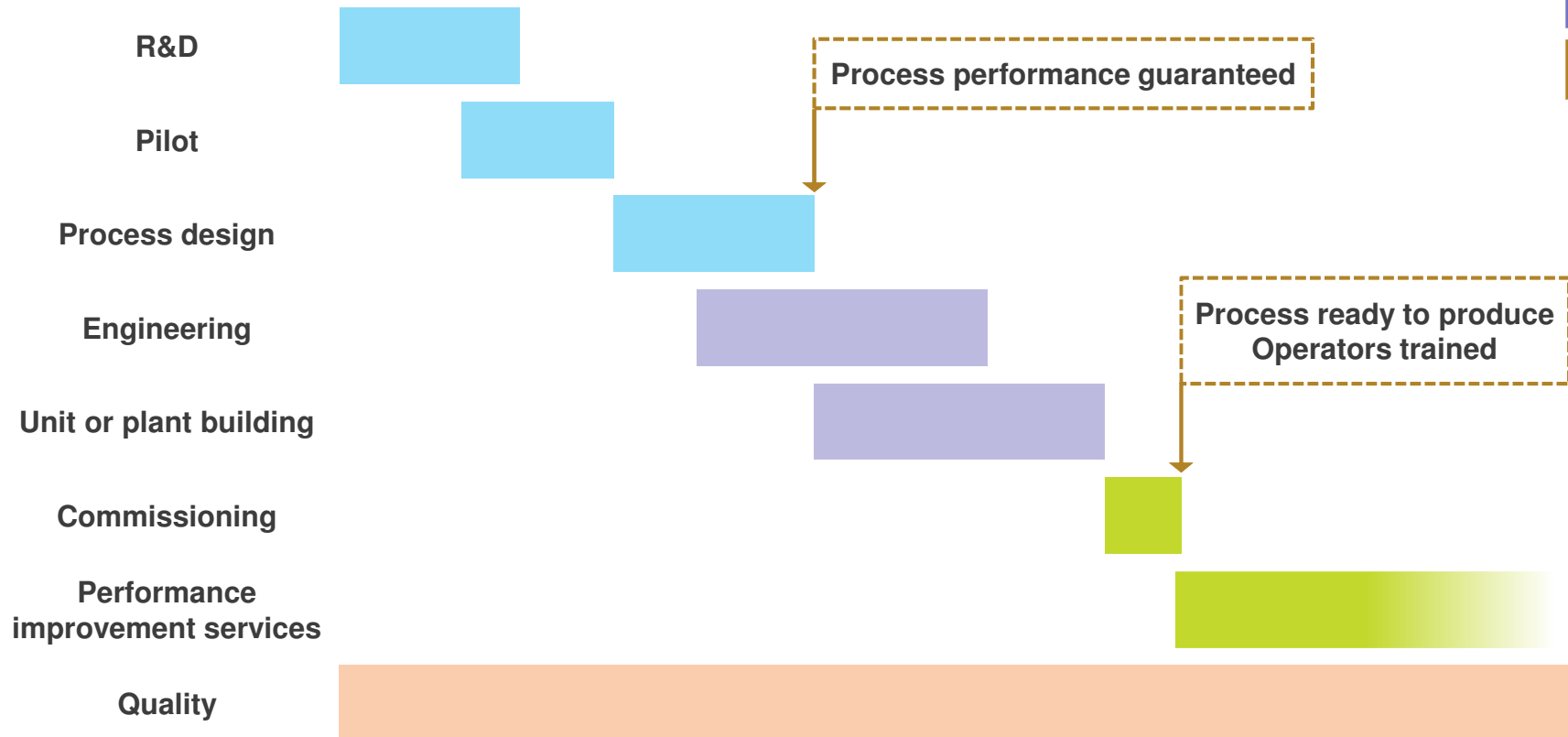
Citric acid



Succinic Acid



From R&D to plant start-up: your project is in good hands



Industrial Biotech Markets

Food Ingredients



- Sugar (beet, cane, liquid)
- Starch derivatives: glucose/fructose syrups for soda, beverages, food
- Milk and whey ingredients (infant milk powder, etc.)

Functional Ingredients



- Food additives with specific action
- Prebiotics: FOS / GOS
- High intensity natural sweeteners (stevia)
- Antioxidants (polyphenols, Anthocyanin)
- Omega 3

Fermentation & Chemical Commodities



- Additives to animal feed (amino-acids, bulk antibiotics)
- Food organic acids (lactic, citric, etc.)
- Bio-based chemical building blocks to replace oil-based chemicals
- Organic chemical commodities

Over **650 industrial references** worldwide
~30 new projects p.a.



Novasep's technology portfolio:

Chromatography



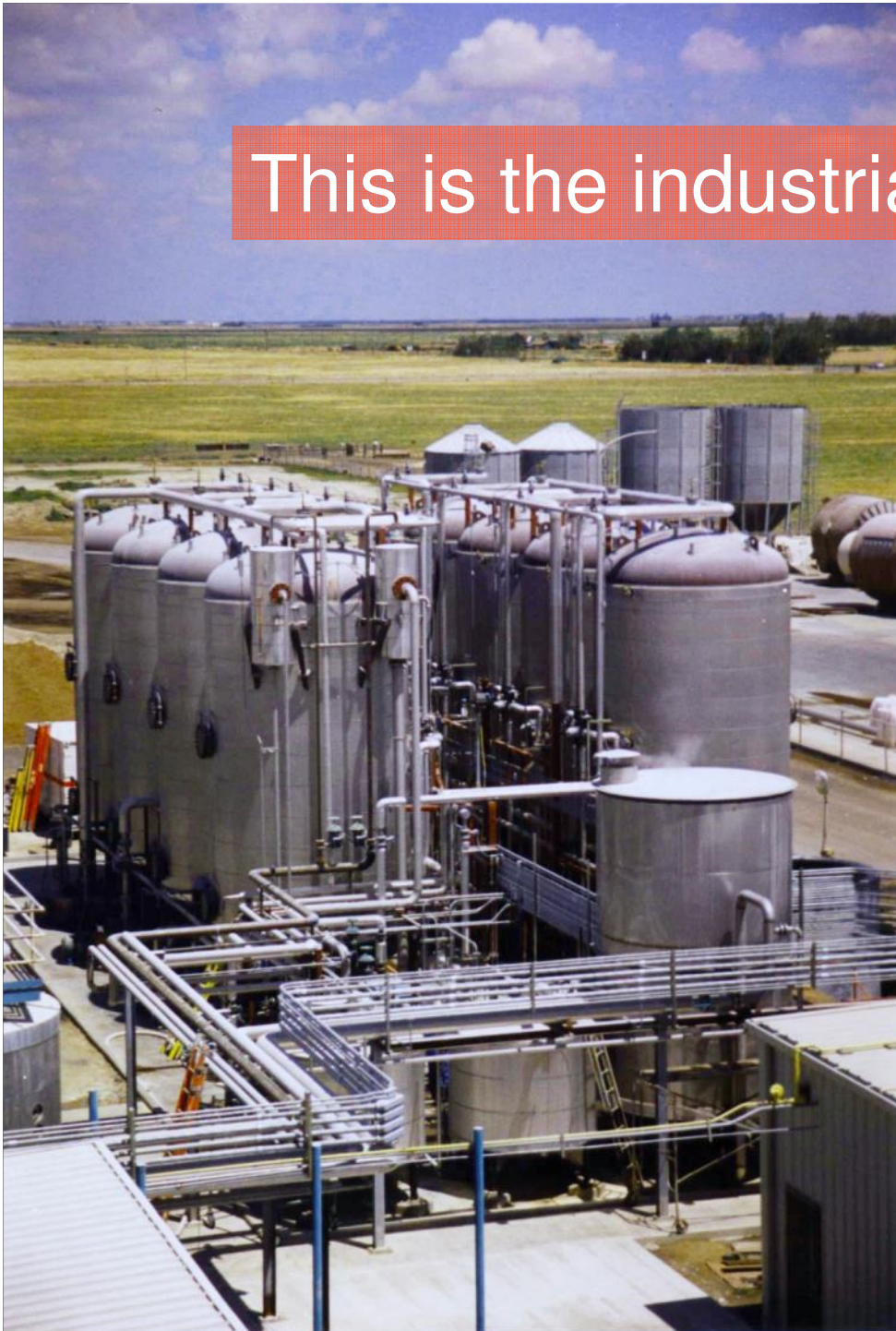
You said chromatography?



HPLC Lab equipment



This is the industrial Applexion® SC!



Applexion® SC

热烈祝贺全国首家F55高果糖浆投产

2号色罐柱

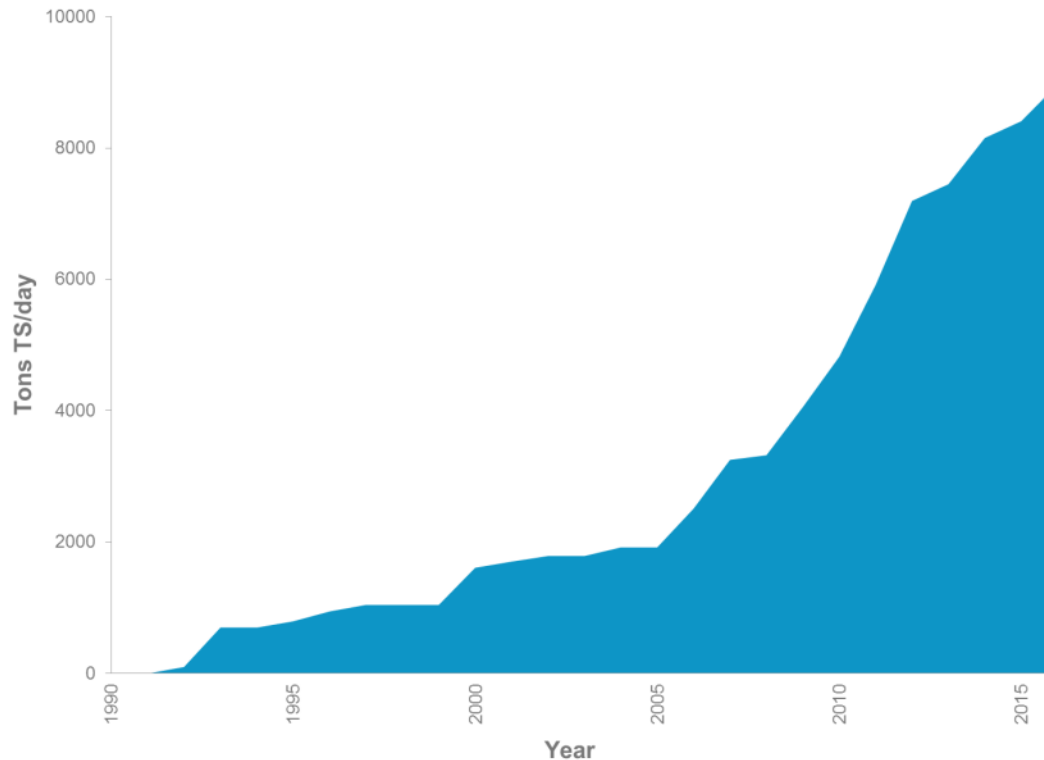
1号色罐柱



Chromatography, an industrial process

Operating in continuous (24/7, 350 days a year)
Low separation cost (1 or 2 cents of euro / kg)

Novasep Industrial Biotech
Low pressure chromatography installed capacity

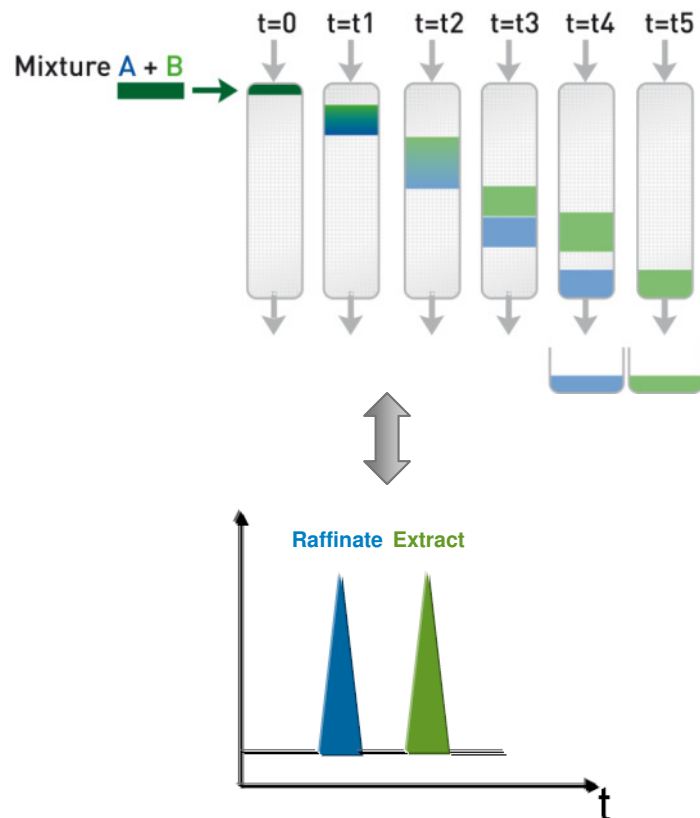


Application examples		
Product	Product price	Installed capacity
Fructose HFCS	0,7 €/kg	1710 kT / y
Citric acid	0,8 €/kg	135 kT / y

Chromatography principle

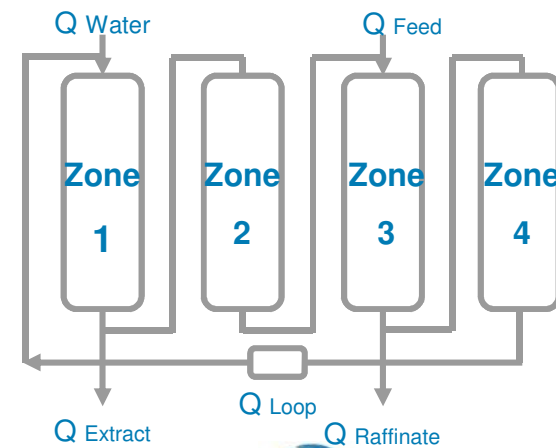
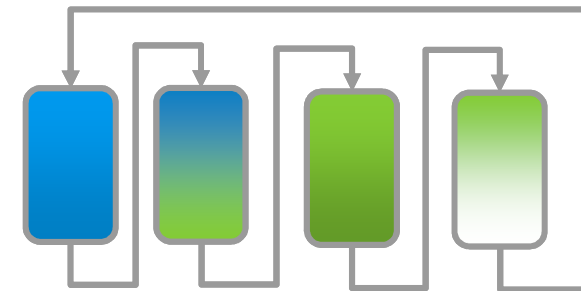
Chromatography principle

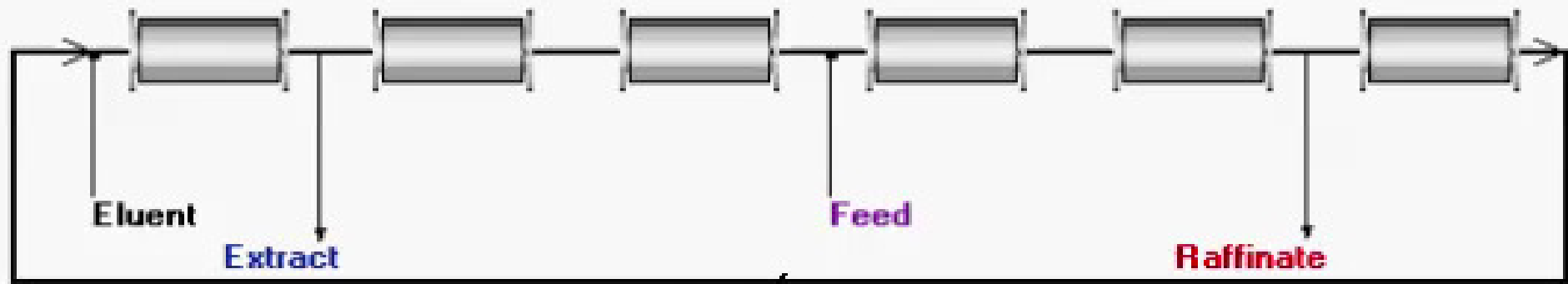
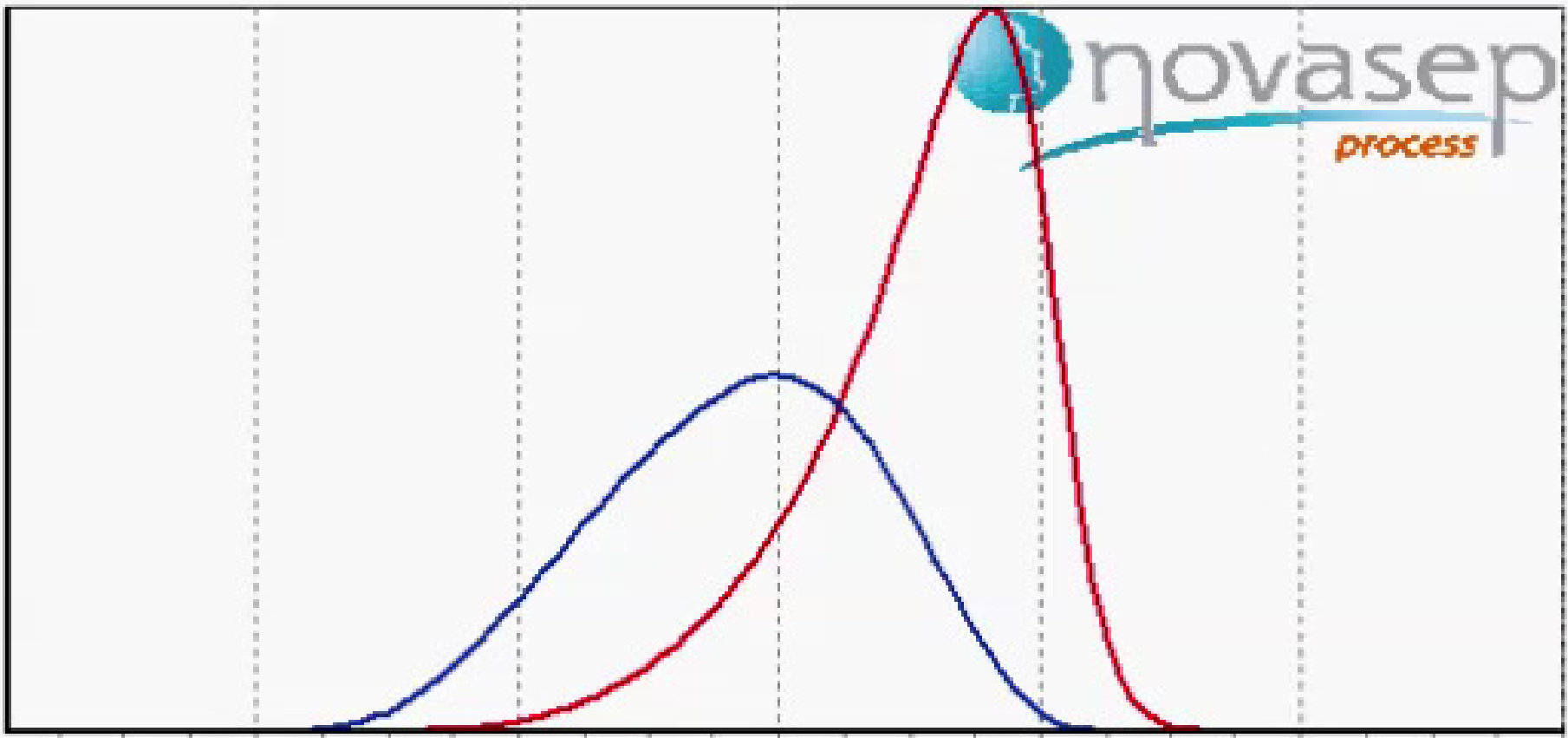
Low pressure liquid chromatography allows to separate two components by using their difference of affinity with a solid adsorbent phase. No regeneration is required.



High purity fractions
Low water usage
No chemical consumption
Operating in continuous,
24/7/350
Cheap separation costs (1-2
cents €/kg)

From batch to continuous chromatography: the industrial process

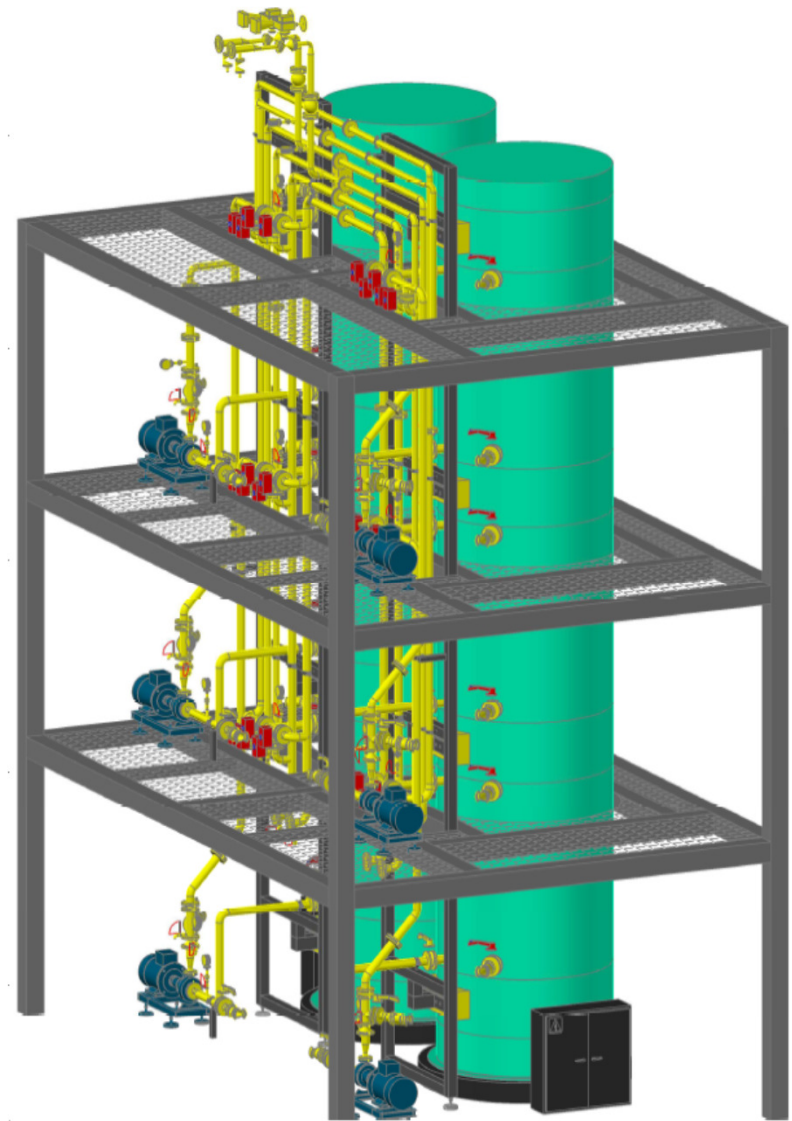




Recycling stream

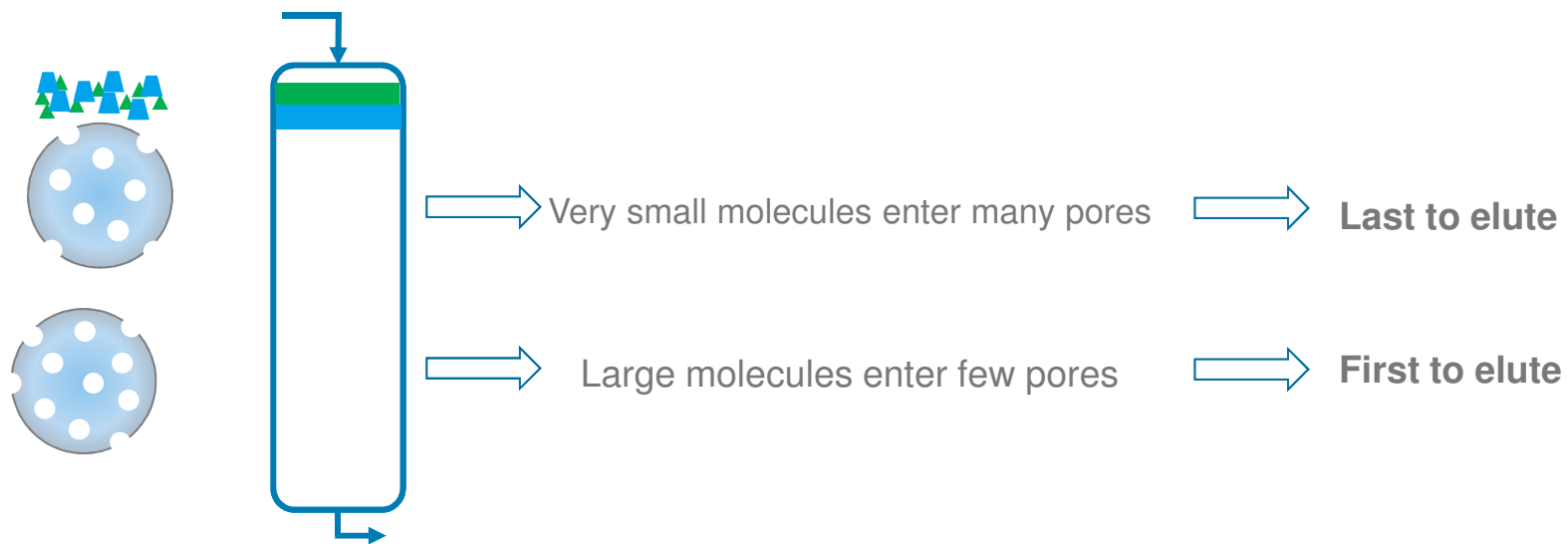
Preparing to collect Red Blue, Inject feed and eluent

Applexion® SC layout



Size Exclusion Chromatography (1/2)

- Separation based on size of the molecules to purify
 - Molecular sieving
 - Porosity of the resin to be adapted to molecular weight
 - Works with strong cation exchangers (monovalent Na⁺, K⁺)



Typical applications

Glucose (C6) – Maltose (C12) separation
Oligosaccharides (GOS, FOS, XOS, maltodextrins):
DPn fractionation



Size Exclusion Chromatography (2/2)

- Product: Galacto-oligosaccharide (GOS)
- Target: DP1 – DPn separation
- 8 references for GOS/FOS

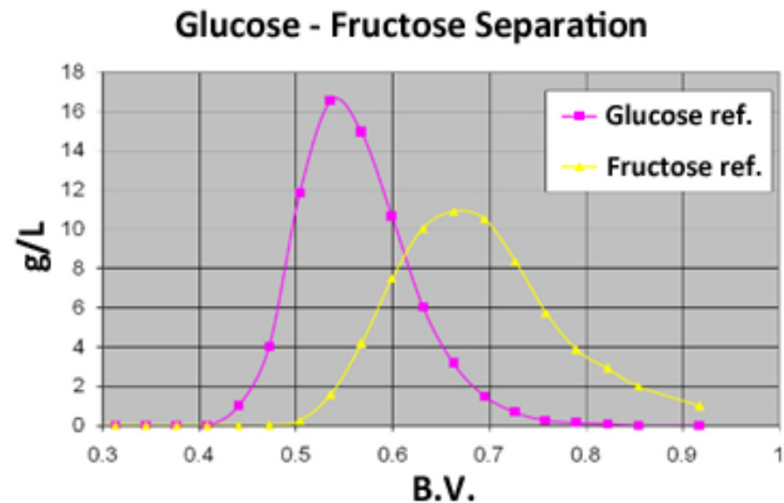
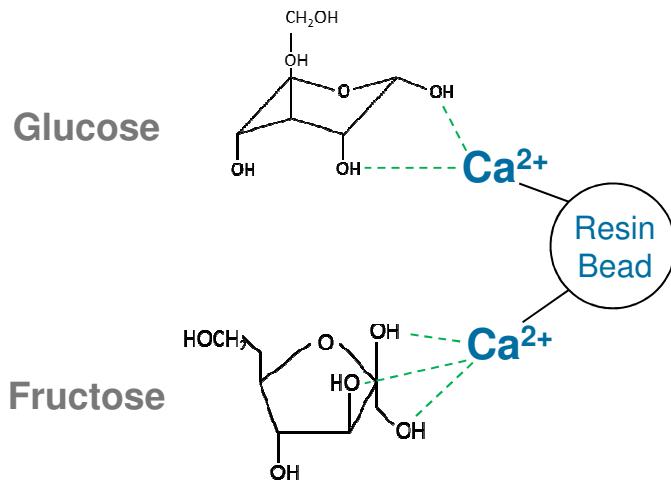


Resin	XA2004/30 Na
Volume of resin installed	45 m ³
Number of columns	6
Column diameter	2.2 m
Daily capacity	18.2 TDS/day of purified GOS 5000 TDS per year
Recovery	> 97% of GOS
Purity	< 5% DP1



Affinity Chromatography (1/2)

- Separation based on specific interactions with the resin
- Ligand exchange
 - Interaction between the resin and the hydroxyl groups (OH) of the sugar molecules
 - Affinity depends on the spatial configuration of the molecule
 - Works with strong cation exchangers (Ca^{2+} , Pb^{2+})



Typical applications

Separation of isomeric monosaccharides (e.g. glucose-fructose)

Separation of polyols (e.g. sorbitol-mannitol)

Affinity Chromatography (2/2)

- Product: HFCS 55 (55% Fructose syrup)
- A proven experience with 32 industrial references

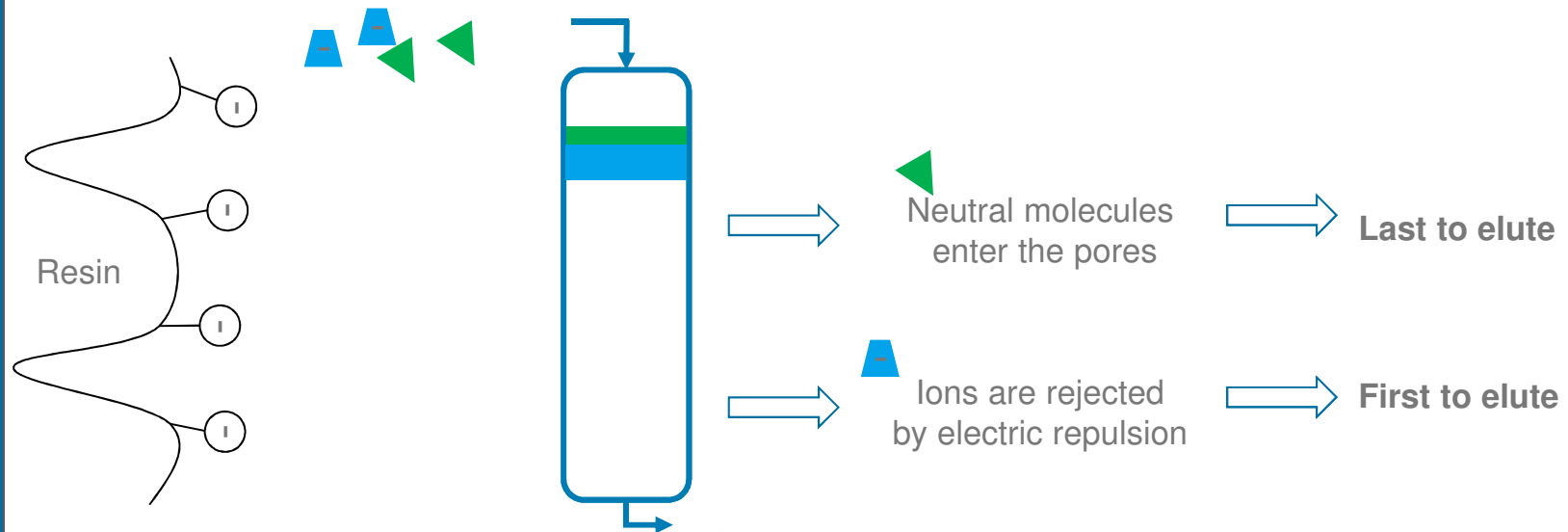


Resin	XA2004/30 Ca
Volume of resin installed	24 to 160 m ³
Number of columns	4 or 6 cells
Column diameter	2 to 5 m
Daily capacity	200 tons DS/day for a 4 cell, 4m Ø SSMB system (101 m ³ total resin)
Fructose recovery	89%
Fructose purity	89.9% (in the extract)

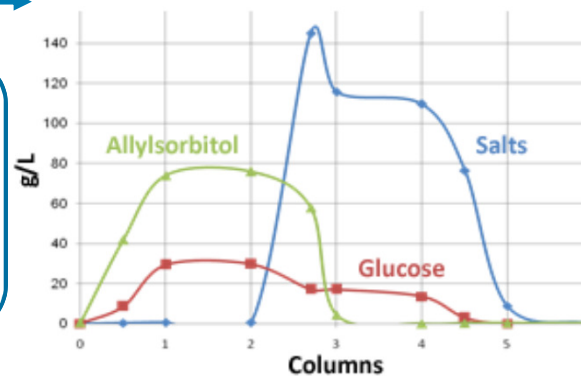


Ion Exclusion Chromatography (1/2)

- Separation based on charge
- Works with strong cation exchangers (monovalent form: Na, K)



Typical applications
Extraction of sugar from molasses
Recovery of lactose from whey
Glycerol and salts separation
Allyl sorbitol demineralization



Ion Exclusion Chromatography (2/2)

- Product: Cane / beet molasses
- 13 engineering and industrial references
 - France, USA, Czeck Republic, Russia
 - 4 NS2P: to recover betaine

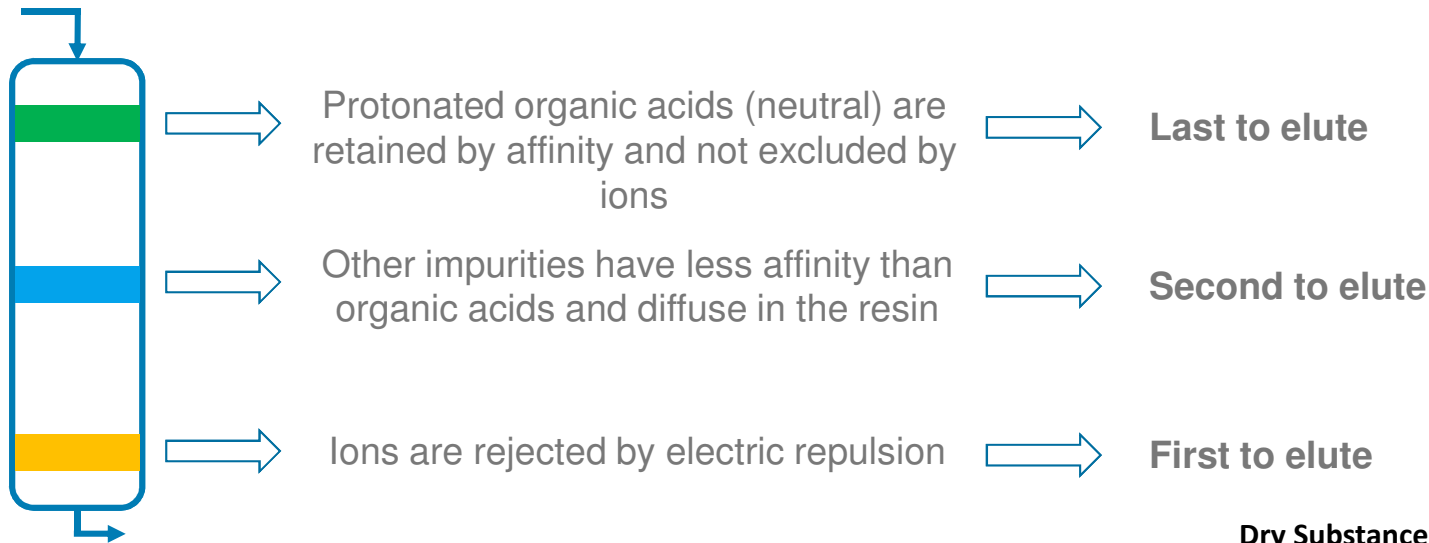


Resin	XA2004/35 K
Volume of resin installed	120 m ³
Number of columns	2 x 3 cells
Column diameter	3.2 m
Daily capacity	96 tonsDS/day
Sugar recovery	93%
Sugar purity	93%



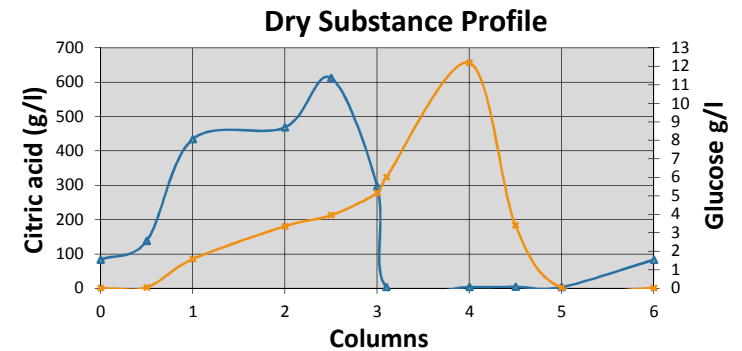
Acid Retardation Chromatography (1/2)

- Separation based on affinity and difference of ionization
- Works with weak base resin (SO₄²⁻ form)



Typical applications from fermentation broth

Citric acid purification
Lactic acid purification
Tartaric acid purification



Acid Retardation Chromatography (2/2)

- Product: Citric Acid
- First plant in the world producing citric acid from biomass designed and built with Novasep
- 6 industrial references
 - 4 in China (2007 – 2012)
 - 2 in Austria (1999 – 2003)



Resin	XA3114/45
Volume of resin installed	120 m ³
Number of columns	2 x 3 cells
Column diameter	3.8 m
Daily capacity	112 tonsDS/day
Citric acid recovery	>95%
Citric acid purity	>95%

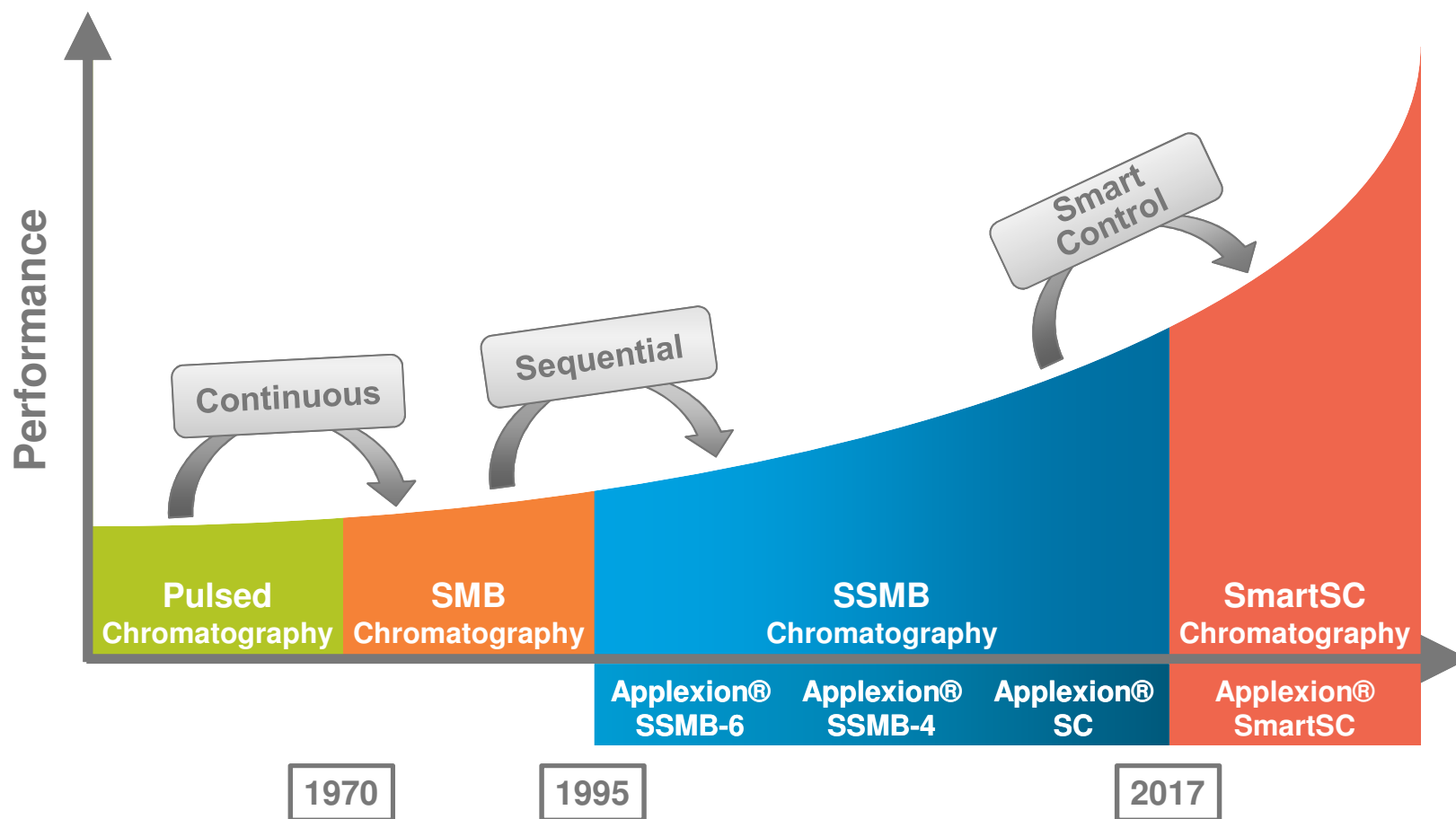




Baolingbao 2006 – 1st Applexion® SC in China



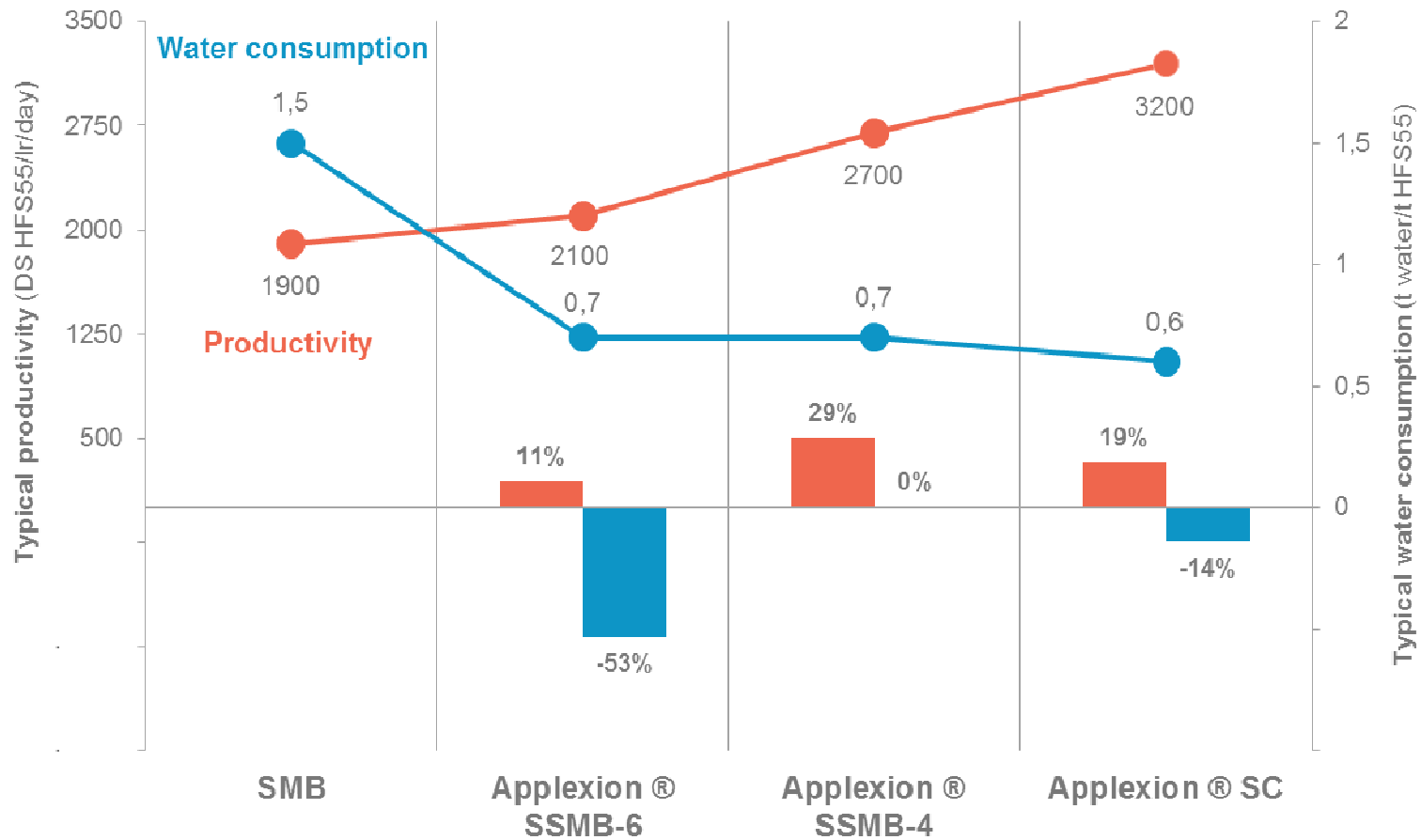
Evolution of industrial chromatography



SMB = Simulated Moving Bed
 SSMB = Sequential Simulated Moving Bed
 SC = Sequential Chromatography

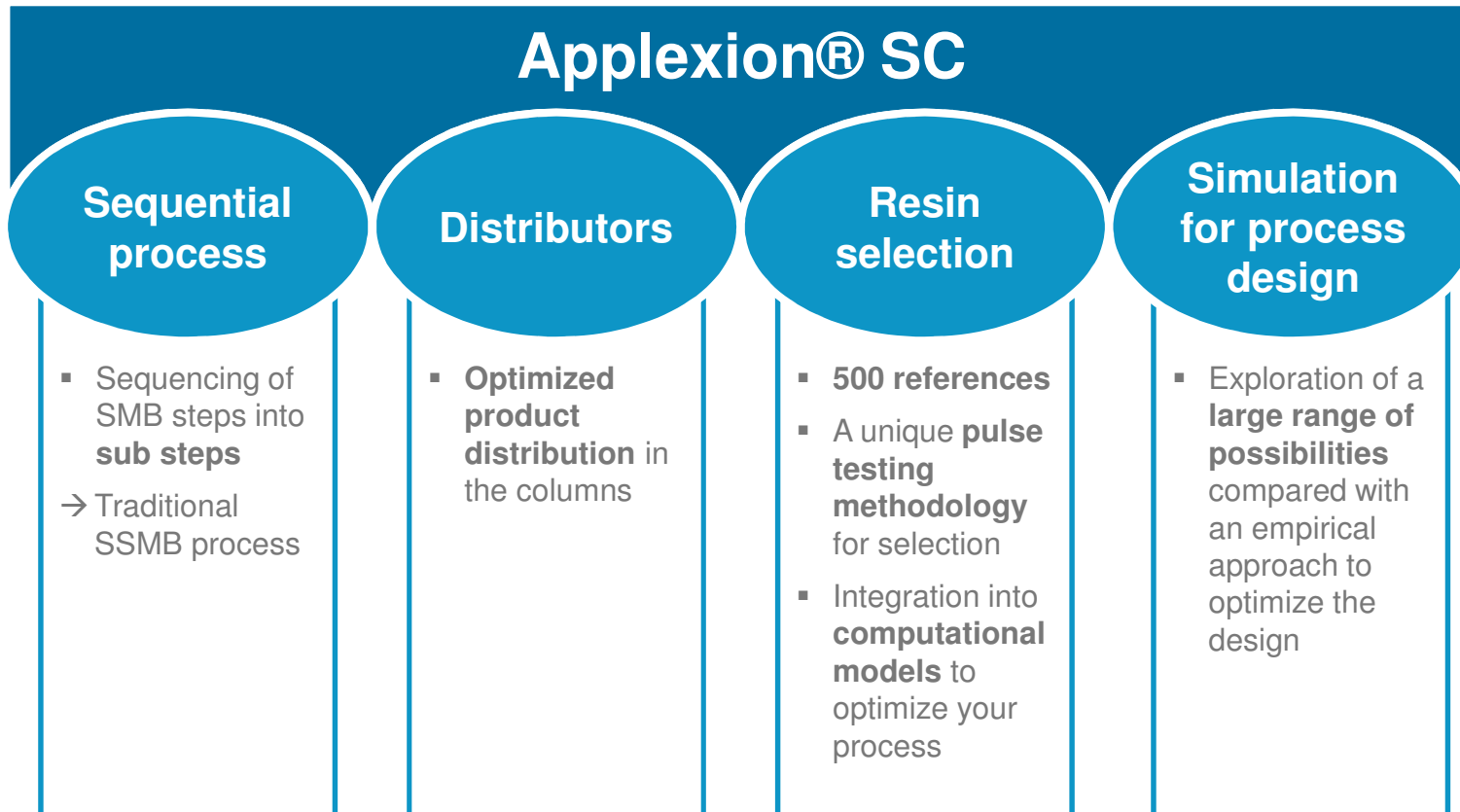
Process performance improvement

Case study: Glucose/fructose separation

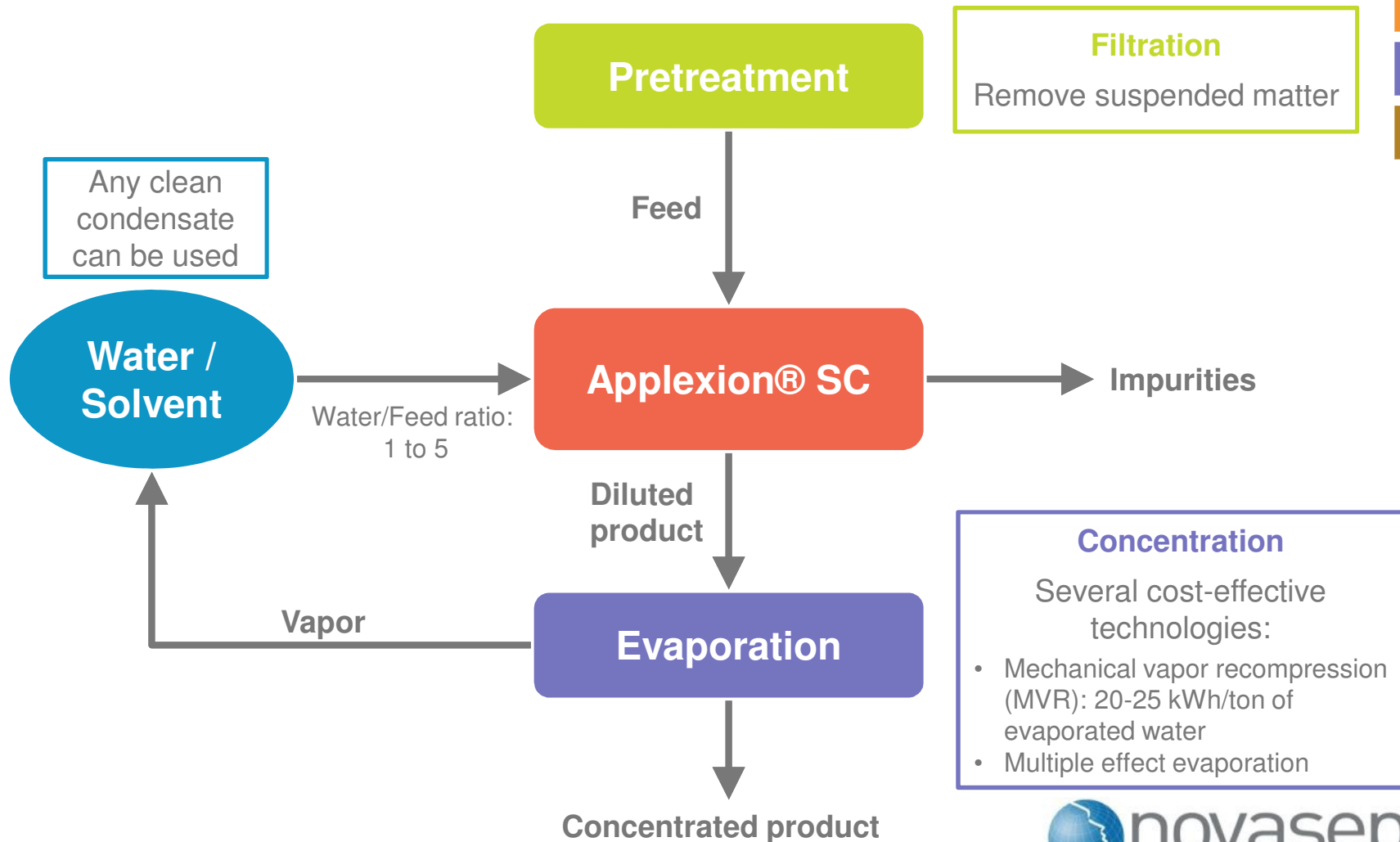


Applexion® Sequential Chromatography

A new step in continuous chromatography



Integration of our technologies in your process



Different principles = new opportunities

Relying on principles different from distillation or crystallization, Novasep's technologies provides new purification opportunities

	Solubility in solvent	Boiling point	Size / molecular weight	Charge (ionic charge, pKa)	H bonds Hydrophobicity	Geometry configuration
Crystallization	✓					
Distillation		✓				
Ion exclusion chromatography				✓		
Affinity chromatography					✓	✓
Acid retardation chromatography				✓	✓	
Size exclusion chromatography			✓			
Filtration			✓			
Ion exchange				✓		
Electrodialysis				✓		



When to use Applexion ® SC?

Substitution or complement to traditional purification technologies



Distillation

- When it is difficult or costly

Thermosensitive products, high or close boiling points, azeotropic mixtures

Examples:

- Organic acids separation from other organics (cyanoacetic acid)
- Polyols separation from salts (pentaerythritol)



Crystallization

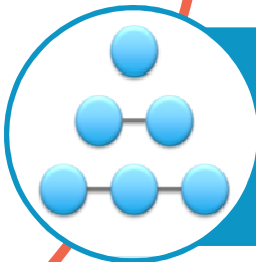
- When it leads to limited yield or purity
- To recover additional product from mother liquor

Organic / salt separation, even if the salt concentration is higher than the product one

Examples:

- Recovery of glycine and methionine from mother liquor

Chromatography efficiency independent of product / impurity ratio



To separate oligomers from monomers

Examples:

- Mono/Di/Trimers of glycerol

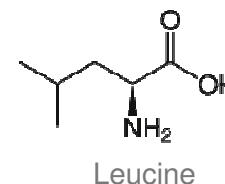
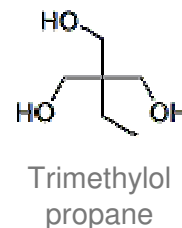
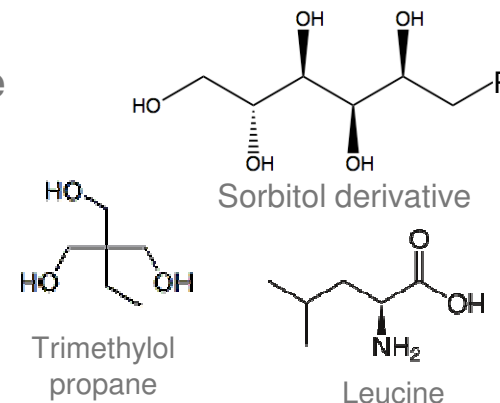
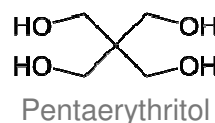
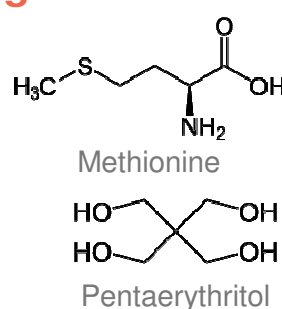
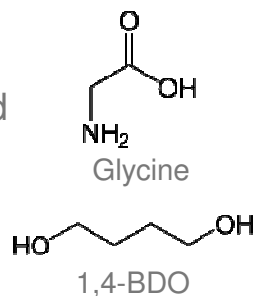


Applexion® SC applications: examples

Ion Exclusion Chromatography

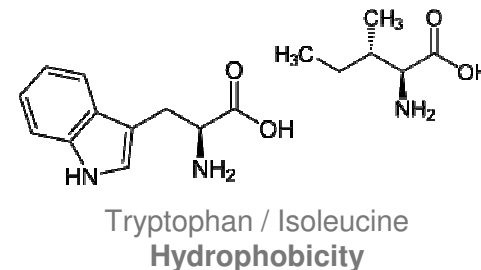
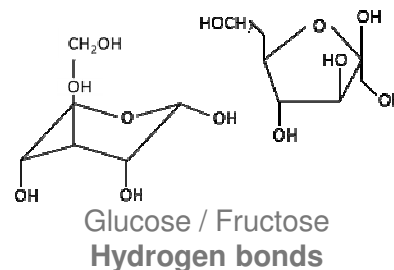
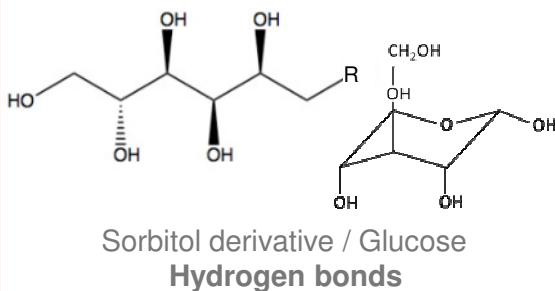
Separation based on the **charge** of the molecule

Neutral molecule
(or zwitterion) and
salt separation



Affinity Chromatography

Separation based on **specific interactions** with the resin

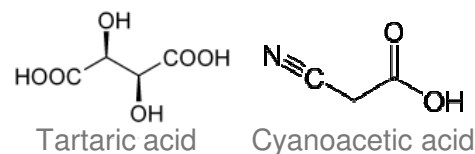
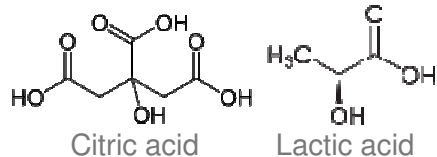


Applexion® SC applications: examples

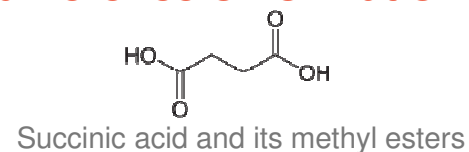
Acid Retardation Chromatography

Separation based on **affinity** and **difference of ionization**

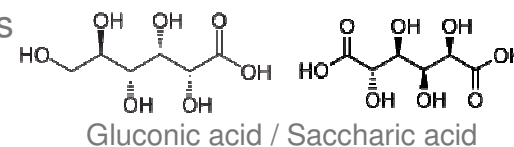
Organic acids separation from other organics and salts



Mono & di-esters separation



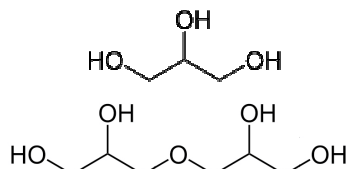
Mono & di-acids separation



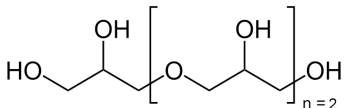
Size Exclusion Chromatography

Separation based on the **size** of the molecules to purify

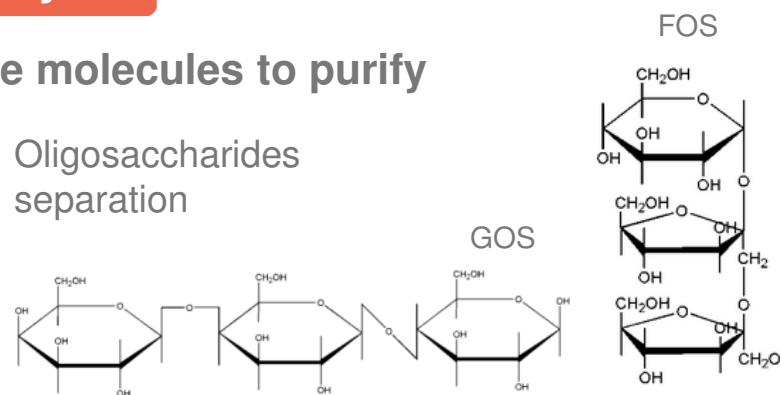
Oligomers separation



Mono, di, tri glycerol



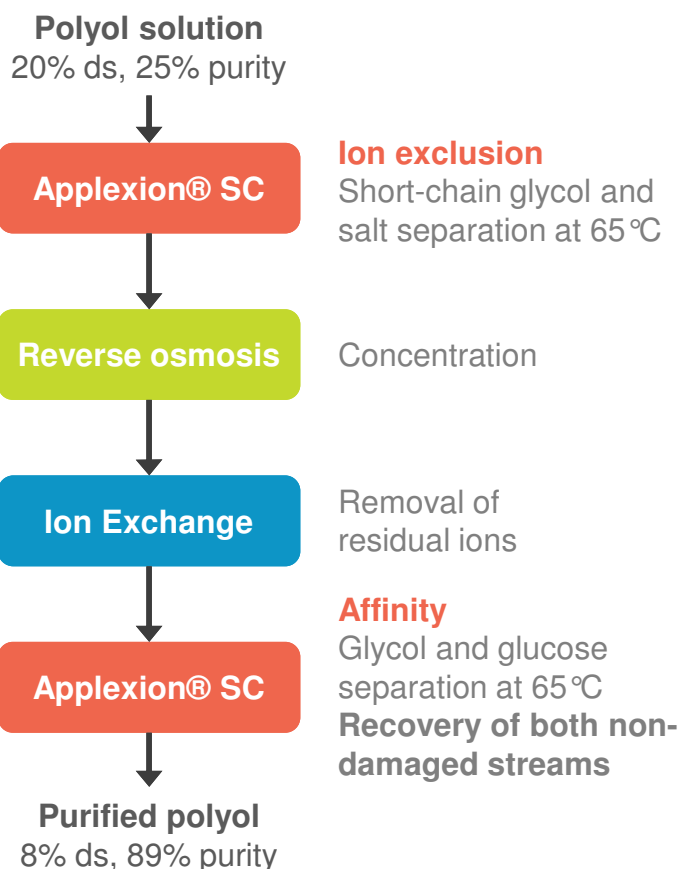
Oligosaccharides separation



Applexion® SC

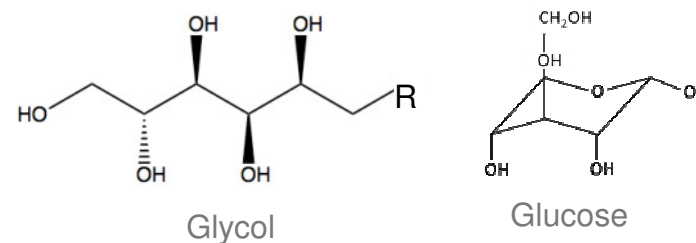
Case study 1: Chemical Polyol purification

Ion exclusion: Neutral molecule / salt separation
Affinity: Hydroxylated molecules (polyol / sugar) separation



Purification of a short chain glycol
(removal of salts and sugars)

Capacity: 20 kT / y

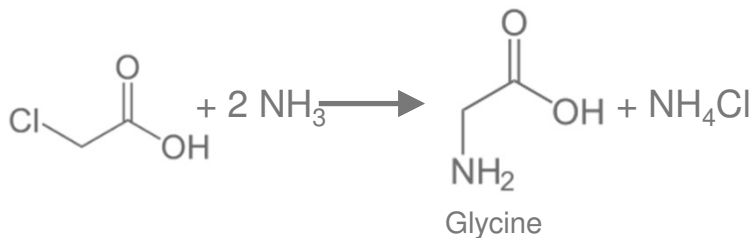


≠ geometries, ≠ interactions with the resin
→ can be separated by chromatography

Applexion® SC

Case study 2: Glycine desalting

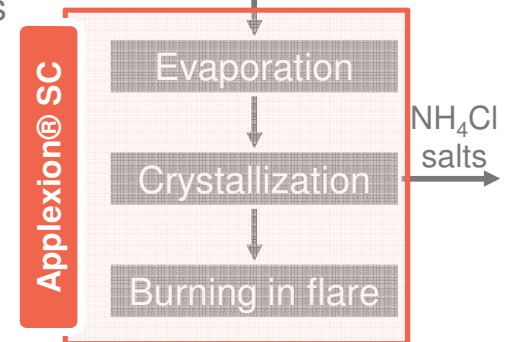
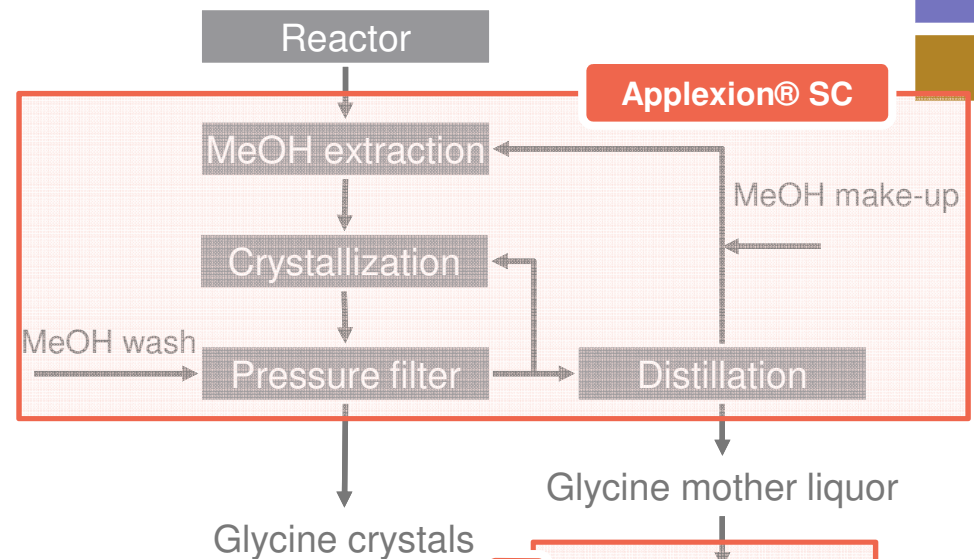
Ion exclusion: Neutral molecule / salt separation



NH₄Cl salt removal from glycine

2 applications:

- **Chromatography on main stream**
 - Strong reduction / removal of MeOH and distillation costs
 - Increased recovery
- **Chromatography for mother liquor**
 - Easy add-on to existing units
 - Recovery increase
 - No flare burning
 - Salts purity increase

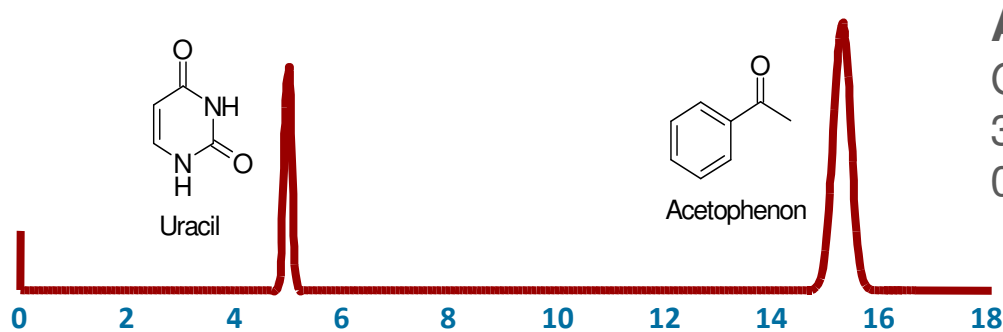


Selection of references

Application	Year	Technologies
Pentaerythritol desalting	2016	Applexion® SC
DL-Hydroxy-Methionine (HMTBa) purification	2016	Applexion® SC
Cyano-Acetic Acid purification	2016	Applexion® SC
DL-methionine desalting	2015	Applexion® SC
Bio-succinic acid	2014	Ion Exchange
Recovery of Glutamic Acid in mother liquor	2014	Applexion® SC
Iminodiacetic Acid mother liquor desalting	2014	Applexion® SC
Glycine mother liquor desalting	2014	Applexion® SC
Aromatic amino acids purification (tryptophan)	2013	Applexion® 3A
MEG desalting	2013	Applexion® SC
Bio-1,4-BDO	2011	Applexion® SC
Bio-1,3-PDO	2011	Microfiltration



From analytical to preparative HPLC

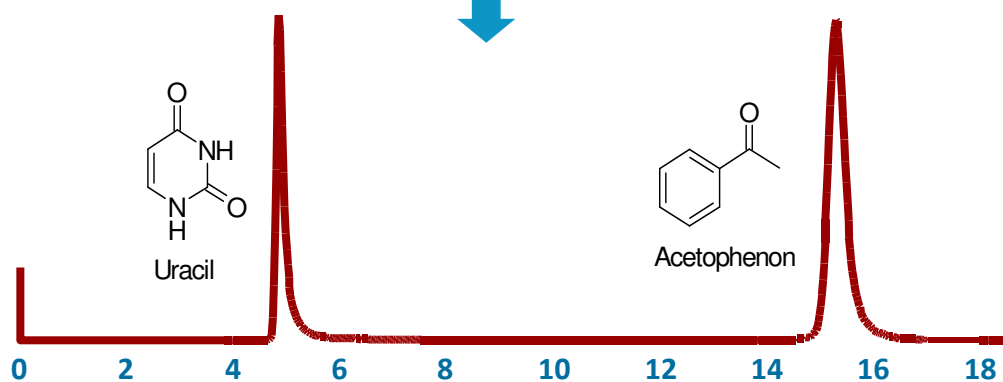


Analytical Column

Column Diameter = 4.6 mm
39,000 plates
0.7 mL/min/m



SCALE-UP FACTOR = 30,000



LC.800.700.VE.70

Column Diameter = 800 mm
42,000 plates/m
1200 L/h

Preparative Chiral Chromatography

Prochrom® Columns Line

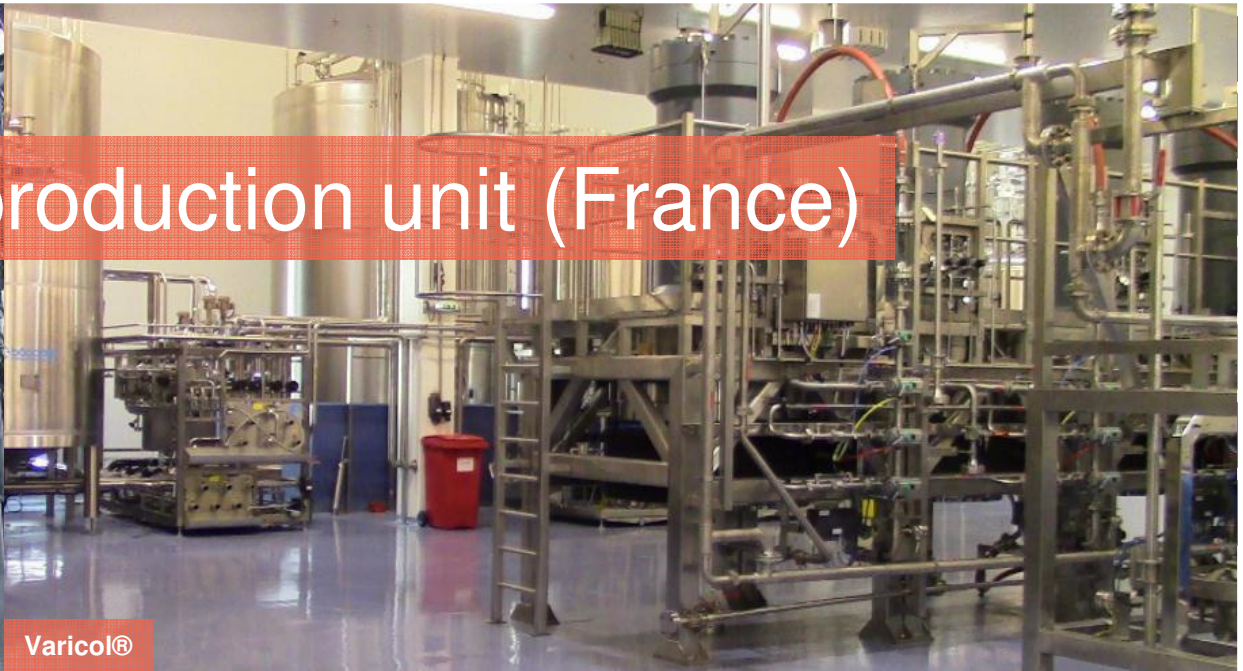


Omega 3 production unit (France)

Varicol®

Evaporator

Varicol®

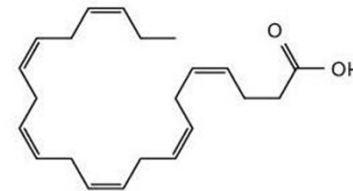


HPLC

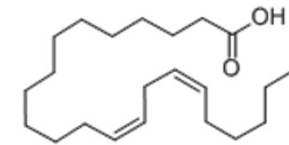
Case study: Fatty acids separations

Affinity: Separation based on molecular geometry

Separation of DHA (DocosaHexaenoic Acid)
C22-6 Omega-3 and C22-2 Omega-6
→ Complementarity of distillation and chromatography



DHA C22-6 Omega-3

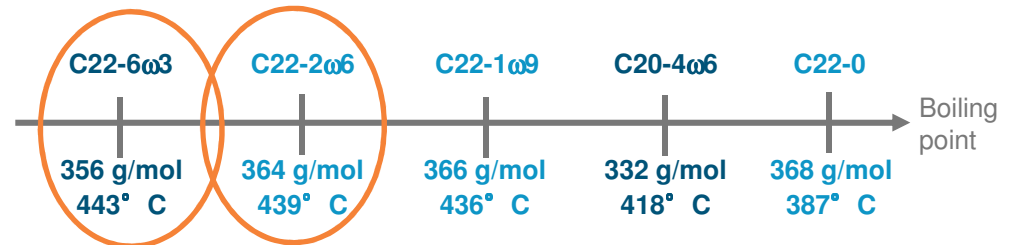


C22-2 Omega-6

Distillation

Separation based on molecular weight and boiling point

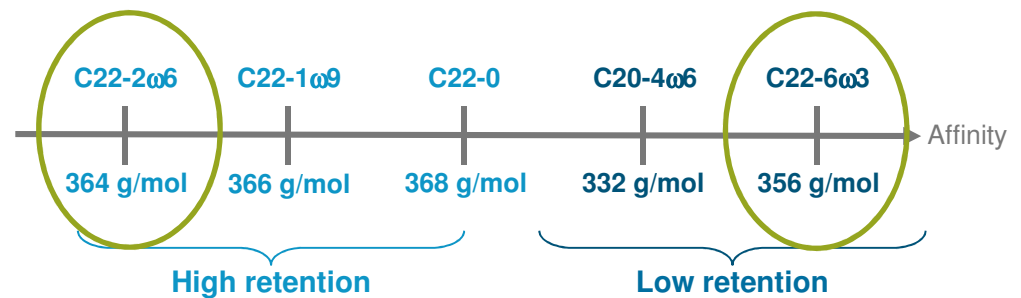
→ Similar behavior of Omega 3 and 6



HPLC chromatography

Separation based on molecular geometry configuration and affinity with a resin phase

→ Easy separation of Omega 3 and 6



Breadth and Depth of our Technology Application



Viral vectors
Gene Therapy
Vaccines, ADCs



Small molecules for
Polymer additives
Cosmetics,...



Small molecules for
Cancer therapy
Diabetes
Etc..



Agro-active
ingredients



Stevia
FOS/GOS
Omega-3



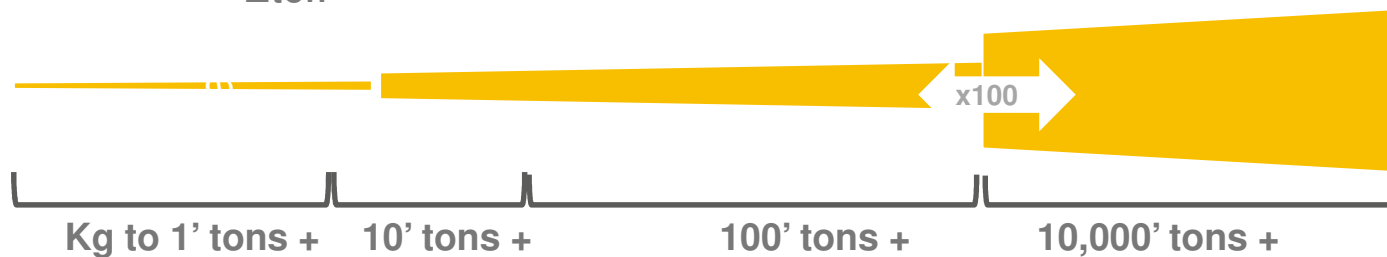
Bio-based
chemicals
Feed ingredients



Sugar
Whey derivatives
Starch derivatives



Scale of
production

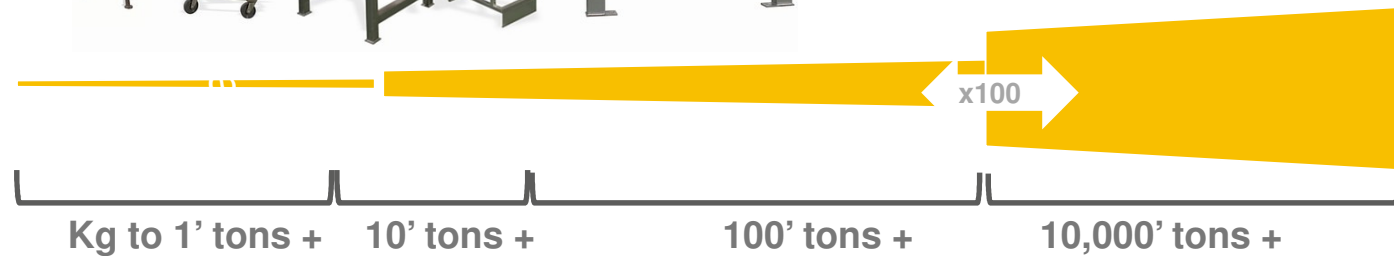


Breadth and Depth of our Technology Application

Example of identical technology but adapted to each scale



Scale of production





Thank you.
Any questions?