Review: Industry Consensus Next Generation Manufacturing Framework: from entry level to advanced processing

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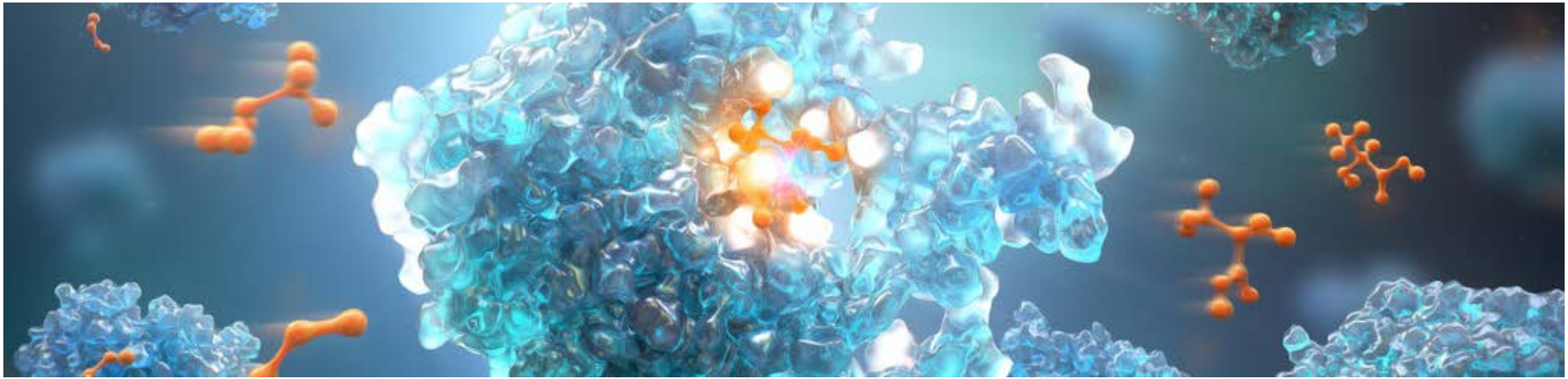
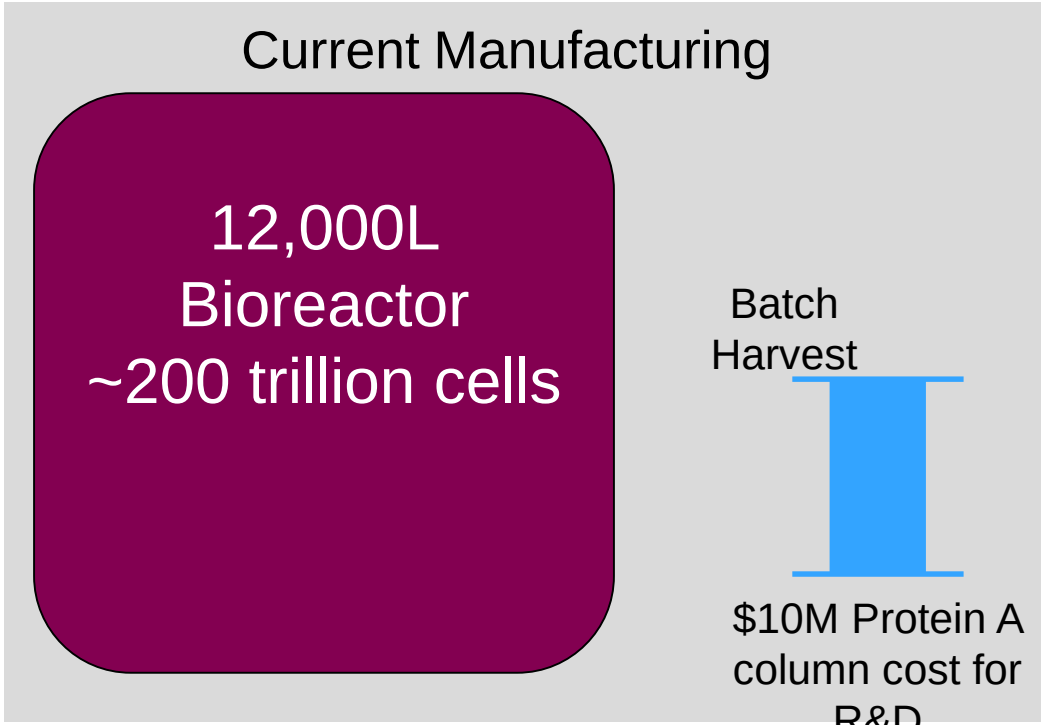


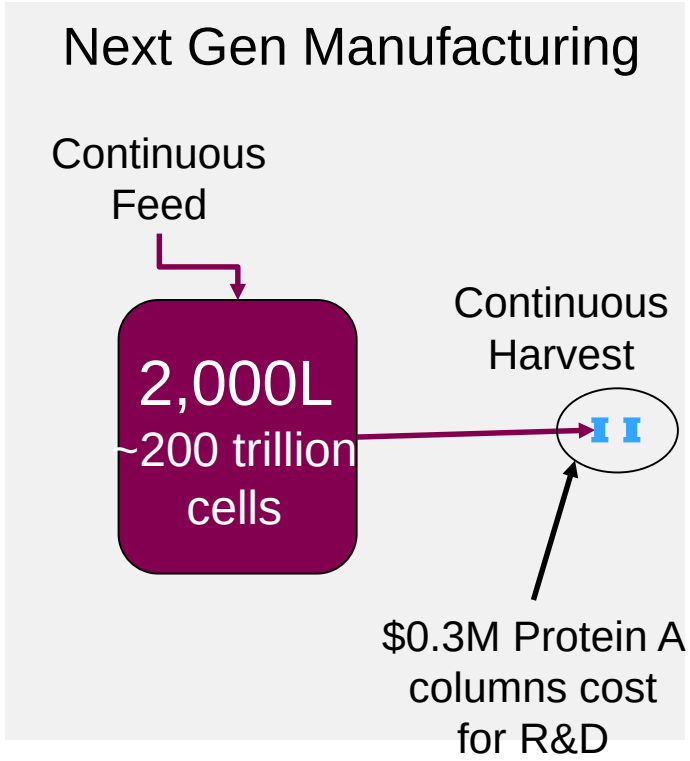
Emerging Industry Framework for Integrated and Continuous rProtein Processing

Target Audience:

- Biopharma Companies new to integrated and continuous processing
- Vendors of integrated and continuous processing equipment
- CMOs supplying integrated and continuous facilities
- Regulators and QA to understand the industry framework of integrated and continuous bioprocessing

NGM concentrates the cells, continuous product harvest





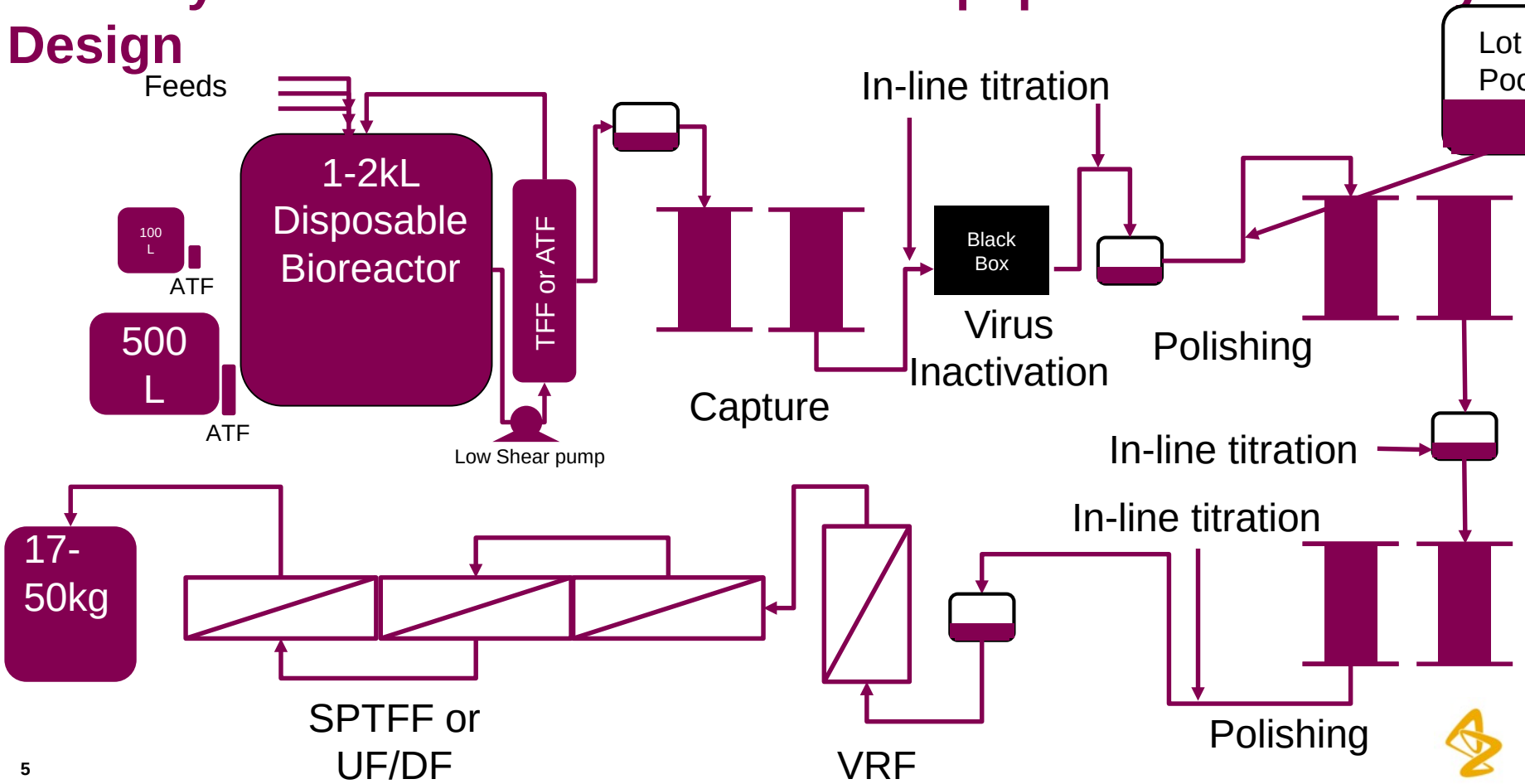
Value:

- Moving from stainless steel bioreactors to single use bioreactors
- Continuous harvest, resulting in a small downstream

Next Gen Manufacturing in the Industry

	N-1	N Brx	# ProA Col.	Virus inact.	#Col. First Polishing	#Col. Second Polishing	Virus Filter	UFDF	GMP?
Amgen	?	Perf	1	Batch	1	1	Batch	Batch	Y
Sanofi	TBD	Perf	≥2	Both	2	2	Cont.	Cont.	Y
Novartis	Perf	Perf	3	Batch	1	0-1	Cont.	Cont.	Y
BMS	Perf	Batch	≥2	Batch	1	1	Batch	Batch	Y
Merck (MSD)	Perf	Perf	≥2	Batch	≥2	≥2	Cont.	Batch	Y
Merck (KgaA)	?	Batch	≥2	Cont.	≥2	≥2	Batch	Batch	Y
Pfizer	Perf	Perf	2	Cont.	1	0	Batch	Batch	N
Bayer	?	Batch	≥2	Cont.	≥2	≥2	?	?	?
AstraZeneca	Perf	Perf	2	TBD	1	0-1	TBD	TBD	N

Industry Common Denominator for Equipment and Facility Design



Stepping Stones to Next Gen Manufacturing

Emerging Industry Framework for Integrated and Continuous rProtein Processing

- Industry has resisted adoption of continuous and integrated processing
- We can propose a step-wise implementation strategy
- Most CMOs can buy entry-level equipment that would satisfy the needs of most of their potential customers
- Biopharmaceutical manufacturers may want specialized and high-end components that can be purchased and installed as needed

Prius: entry-level electric

Tesla: high end electric

Perfusion
Harvest Pool
1 Column Capture
Pool
Virus Inactivation
Batch Polishing
Pool
Batch Polishing
Pool
Virus Filter
Pool
UFDF

ool

Perfusion
2 Column Capture
Cont.Virus Inact.
1-col. Polishing
1-col. Polishing
Virus Filter
UFDF

One dual-column skid

Perfusion
2 Column Capture
Cont.Virus Inact.
2-col. Polishing
2-col. Polishing
Virus Filter
UFDF

Wanted: Off the Shelf Equpment

Perfusion
8 Column Capture
Cont.Virus Inact.
8-col. Polishing
8-col. Polishing
Virus Filter
UFDF

Perfusion Media v1.0 based on Fed Batch Media

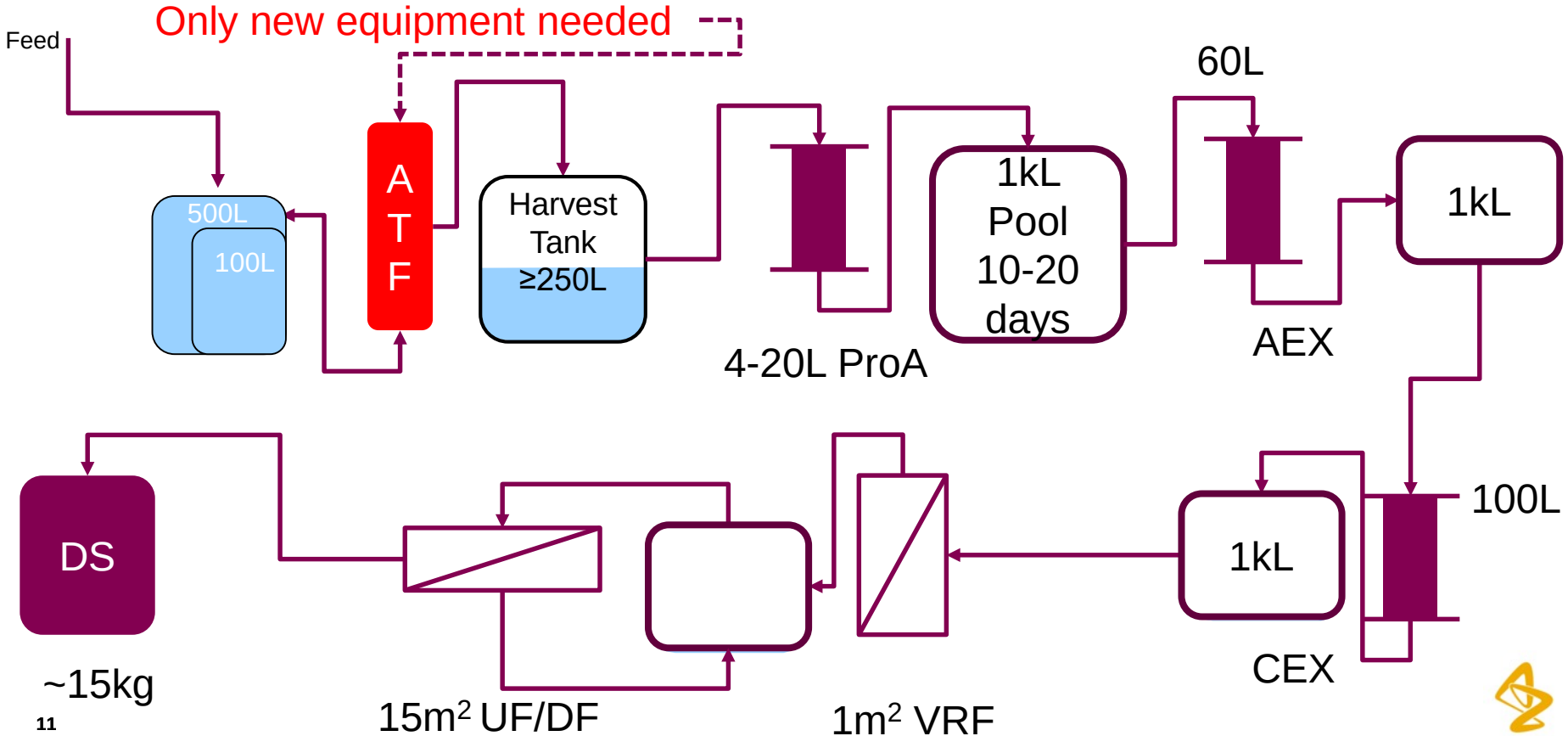
First generation perfusion media mixed from basal and feed medias
Start with
% Feed media = ~% Feed used in batch *(Perfusion Cell Density)/(IVCD_batch)

Perfusion media likely made up of : 5%-10% fed batch feed media and 90-95% basel media

Concentrate perfusion media

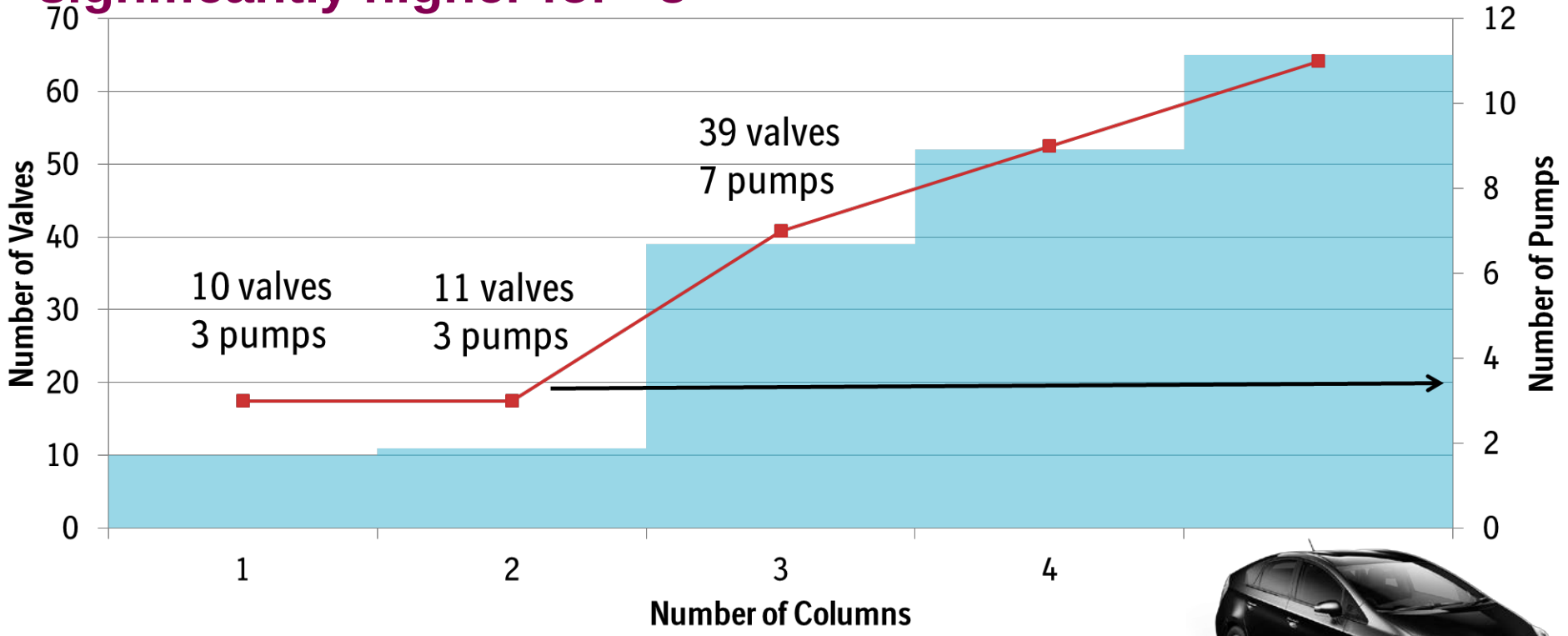
Remove all added salt from Perfusion Media 1.0
Remove buffers
Split media into two to four compatible media concentrates (see Life Tech 1992 patent)
Test varying amount of water as diluent to control the metabolic inhibitors

STAGE 1: Integrated and Continuous Processing in a standard fed-batch plant: use existing equipment



How many columns?

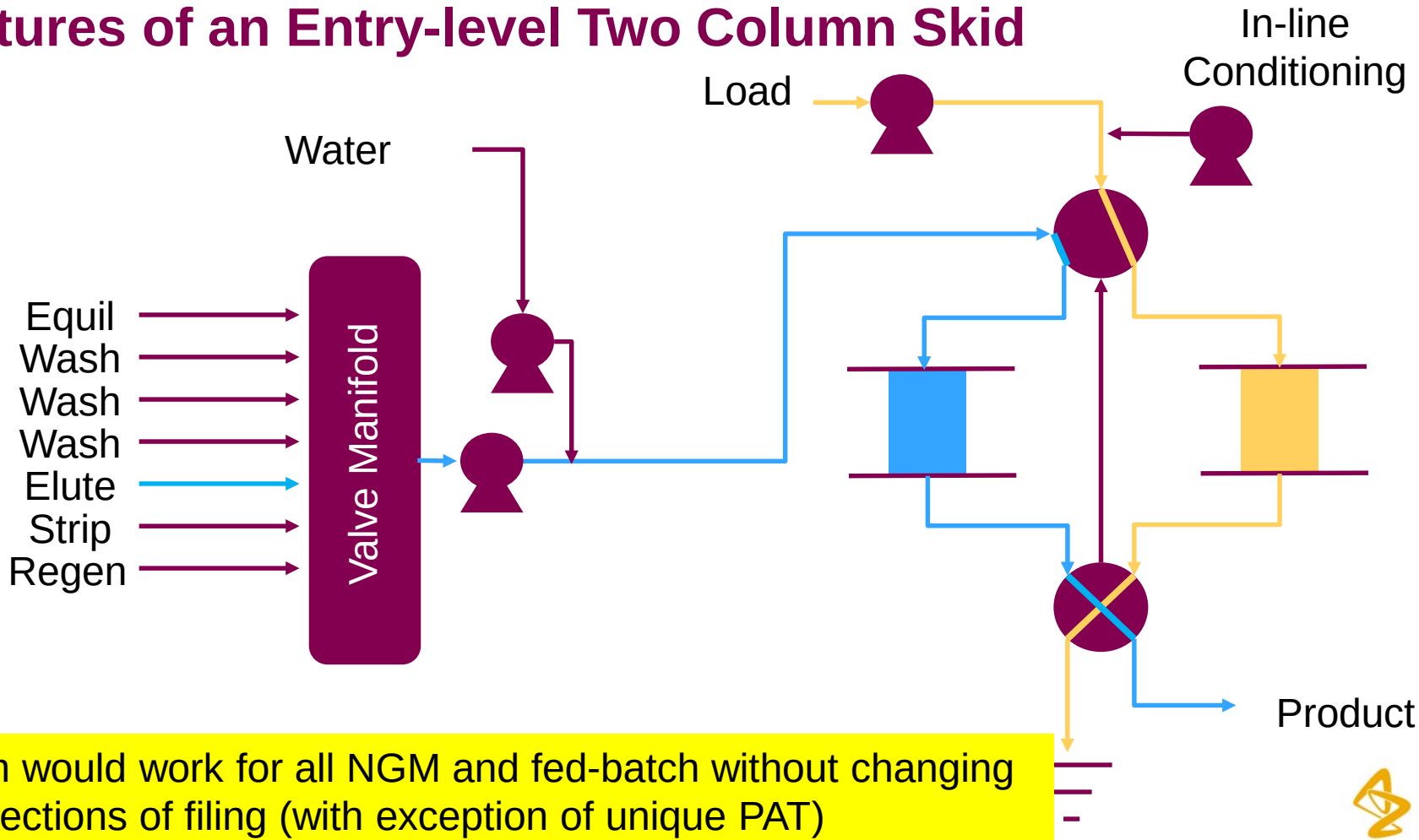
Skid complexity is low for one or two columns; significantly higher for >3



The Entry Level Prius Version of NGM is Two Columns

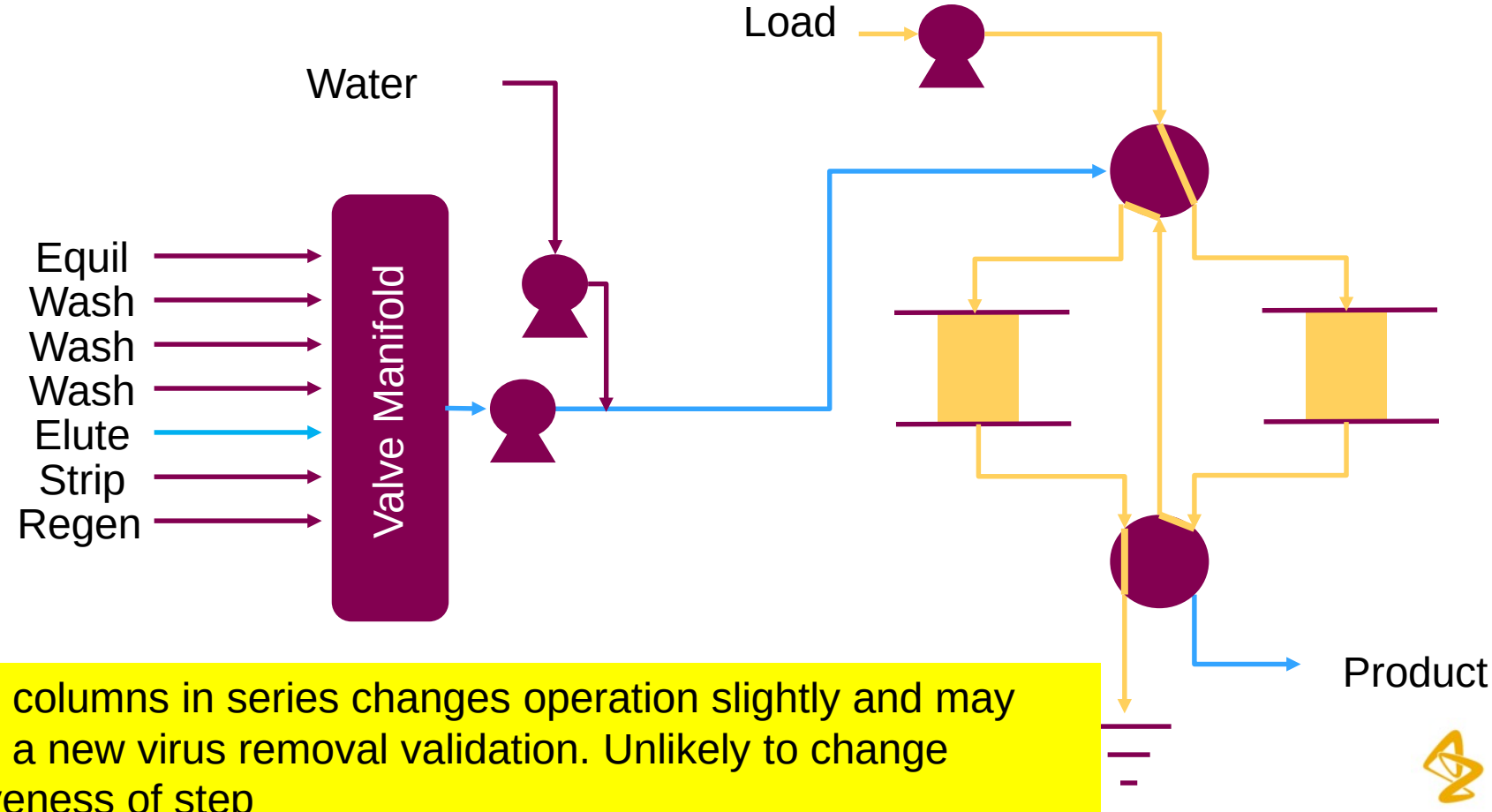
All new chrom skids should be capable of two-column processing for both batch and NGM

Features of an Entry-level Two Column Skid



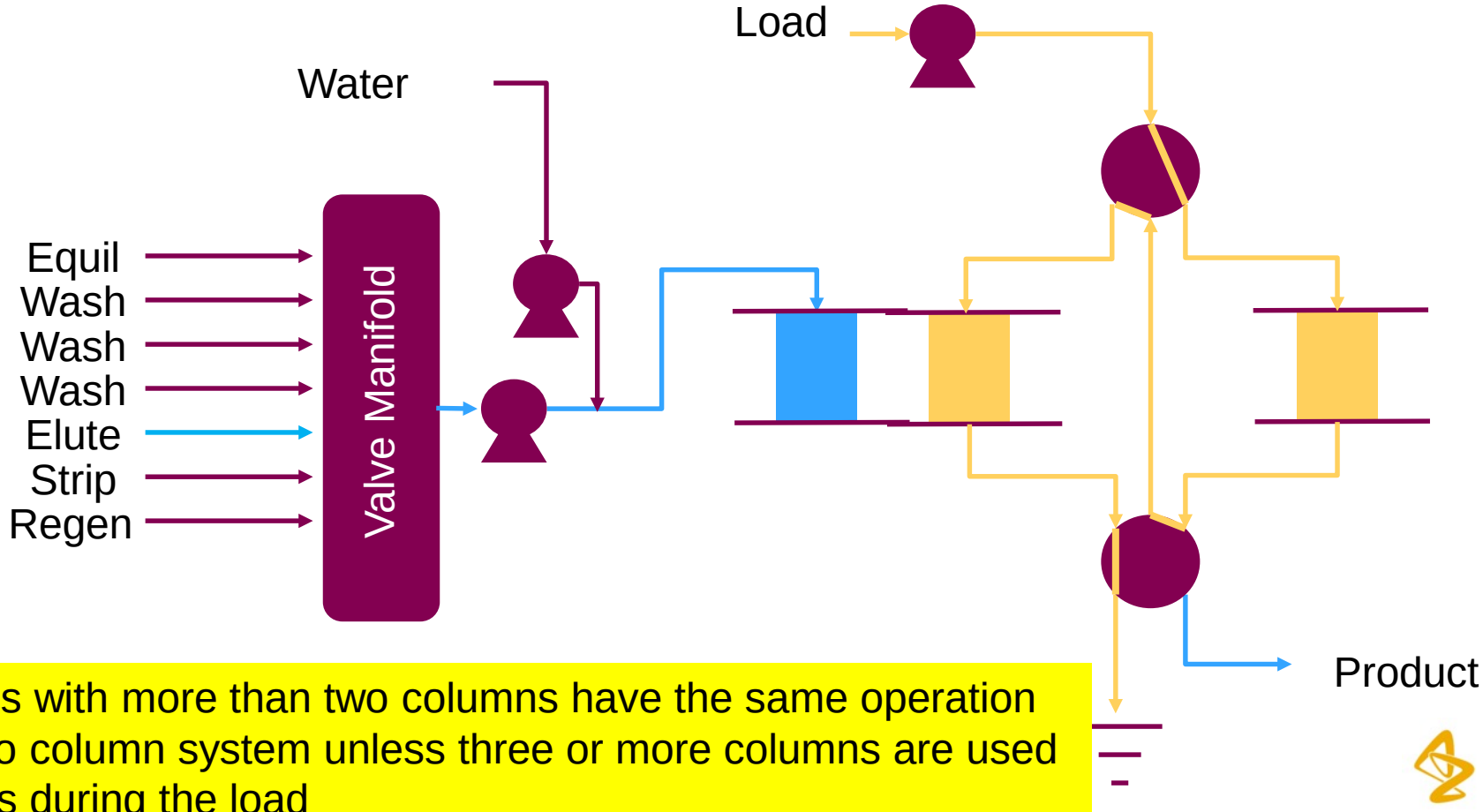
System would work for all NGM and fed-batch without changing CMC sections of filing (with exception of unique PAT)

Some dual columns operated in series during load



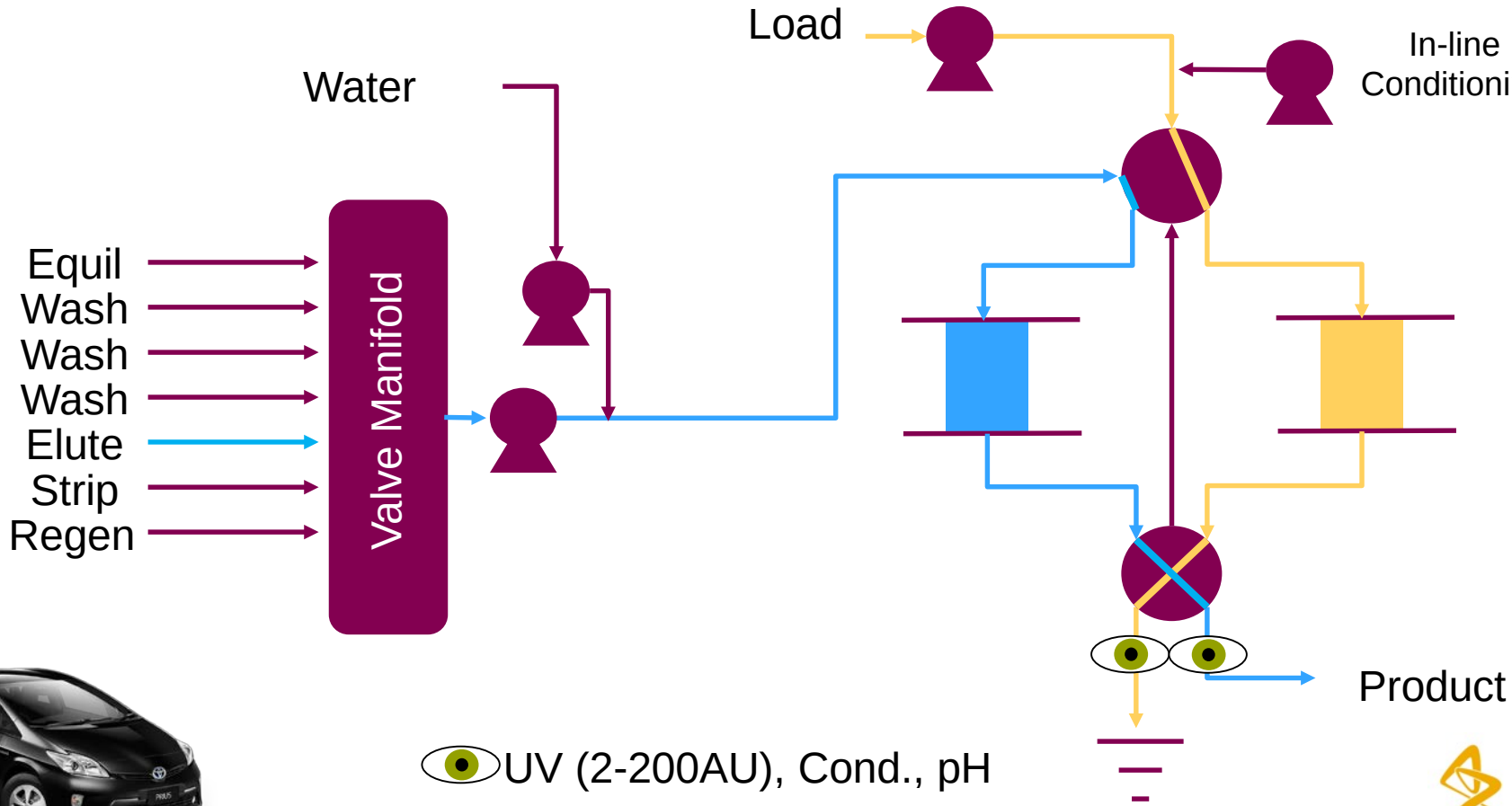
Putting columns in series changes operation slightly and may require a new virus removal validation. Unlikely to change effectiveness of step

Three or more column systems are the same as dual

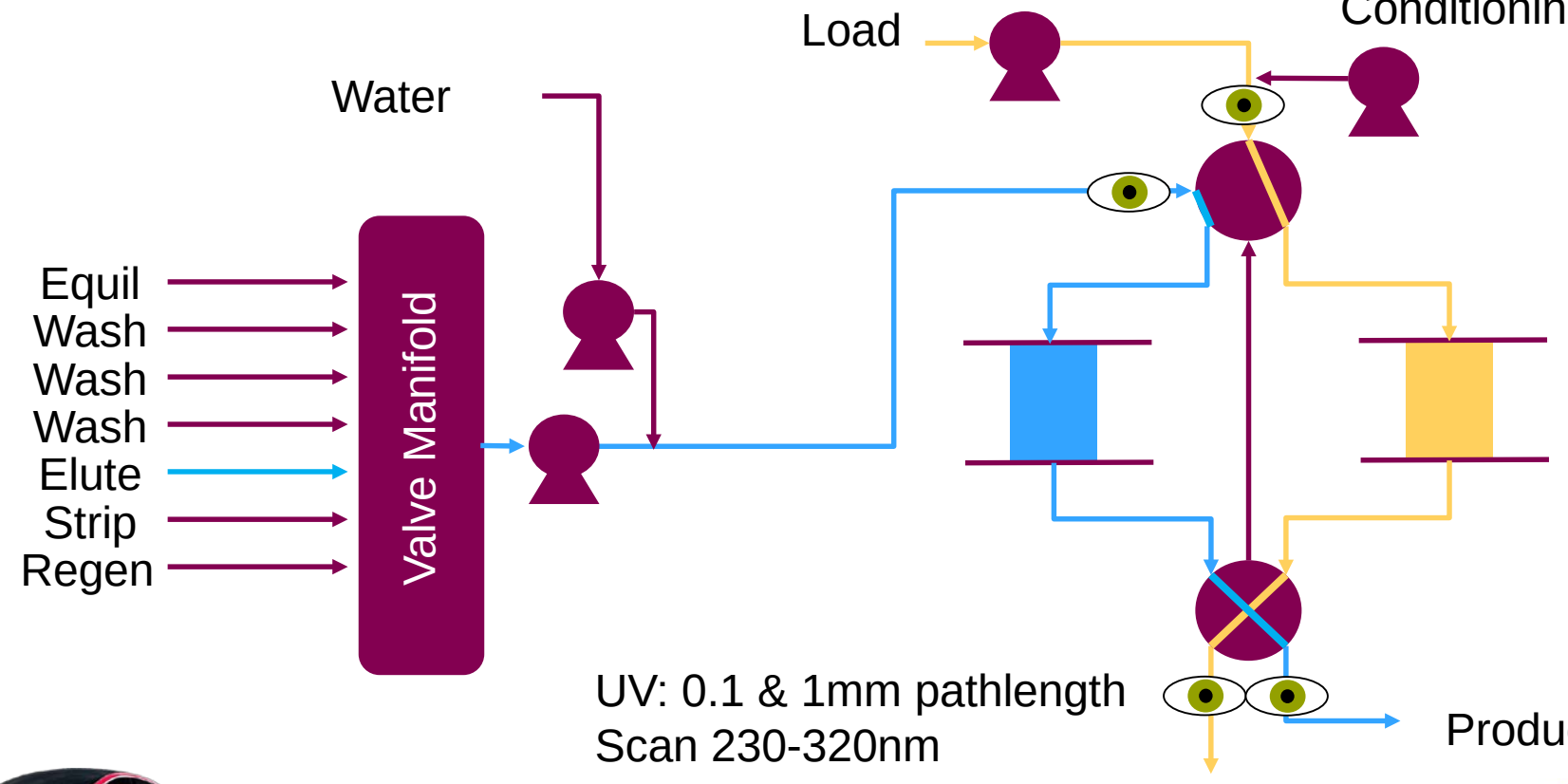


Systems with more than two columns have the same operation as a two column system unless three or more columns are used in series during the load

Sensory Features of a Entry-level Two Column Skid

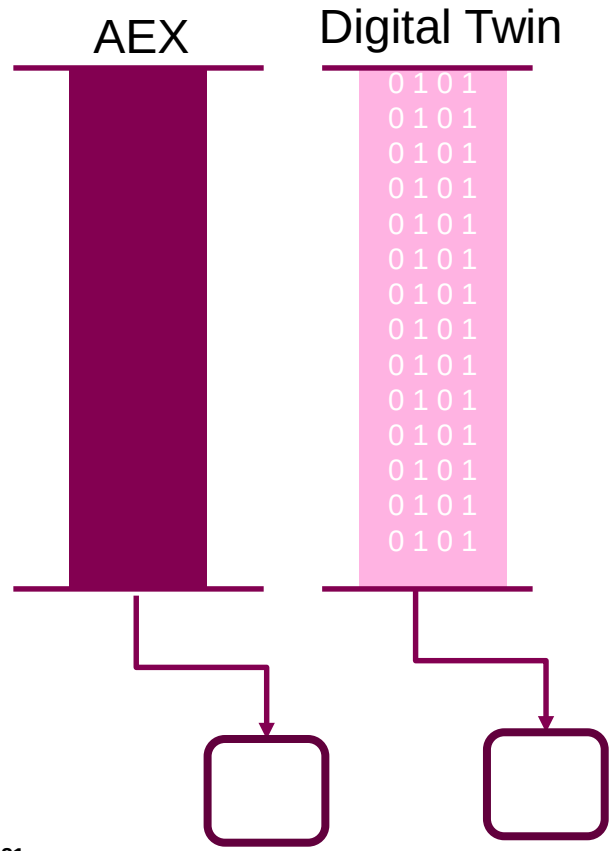


Sensory Features of a Luxury Two Column Skid



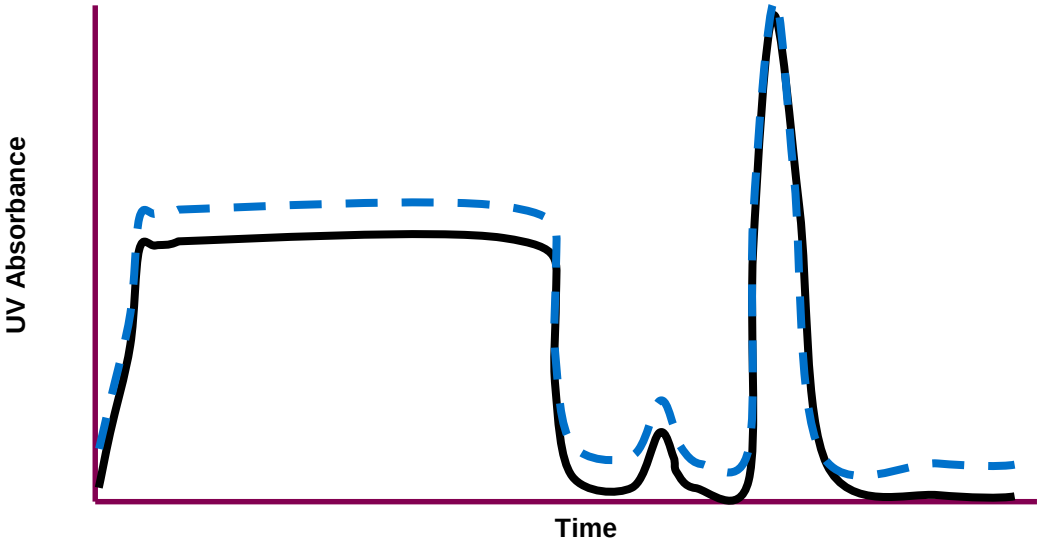
Additional sensors on inlets can allow real-time modelling to assure step operated as intended

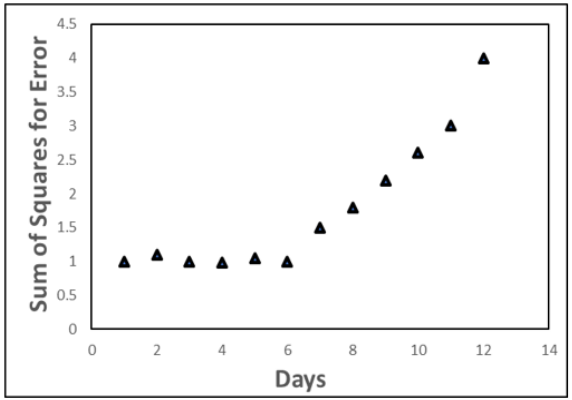
Mechanistic modeling for chromatography



- Diagnose out of spec events
- Supports trouble shooting in manufacturing
- Cut costs in bioprocess development
- Can be used as a PAT tool for making robust pooling decisions

Mechanistic modeling for chromatography



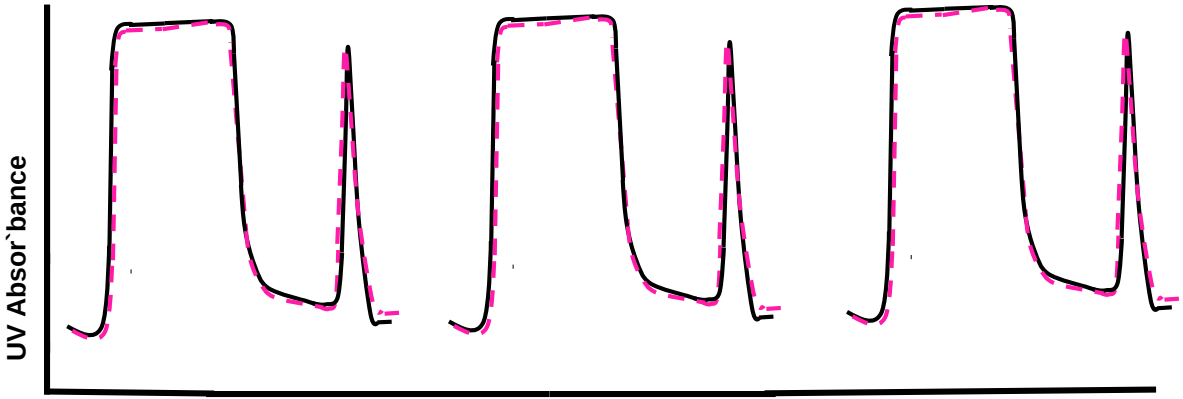


$$\alpha \frac{\partial C_i^i}{\partial t} = \vec{\nabla}.\left[(D_d^s + D_e^s)\vec{\nabla}C_i^i + \vec{u}_i^s C_i^i\right] + R_i^s + \text{Error} + \text{Unknown Physics}$$

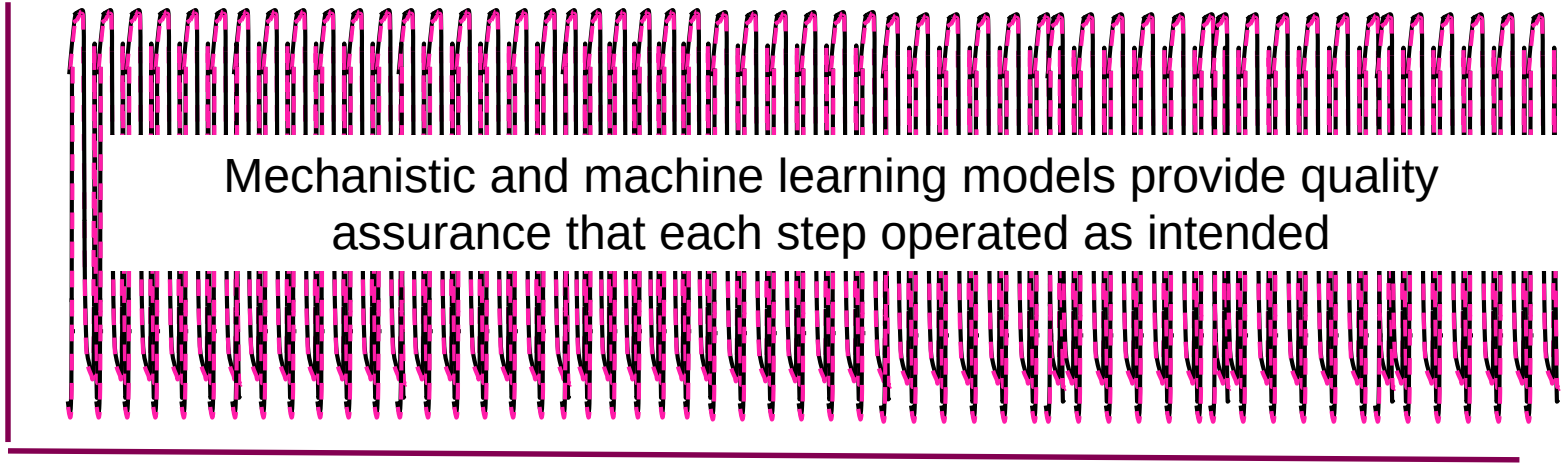
Mechanistic model

Machine learning

NGM generates more data



Batch

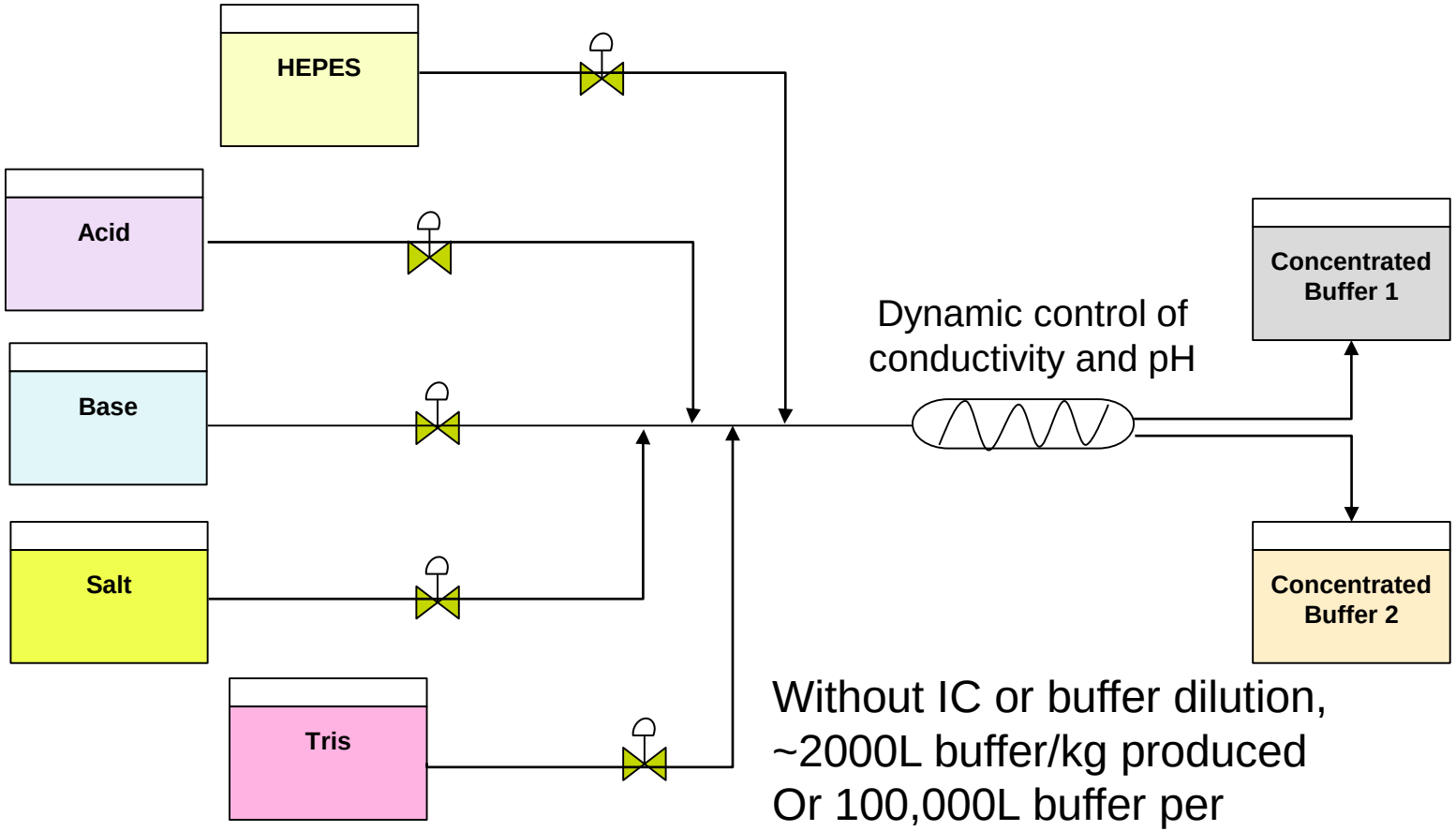


NGM

Sensors and data

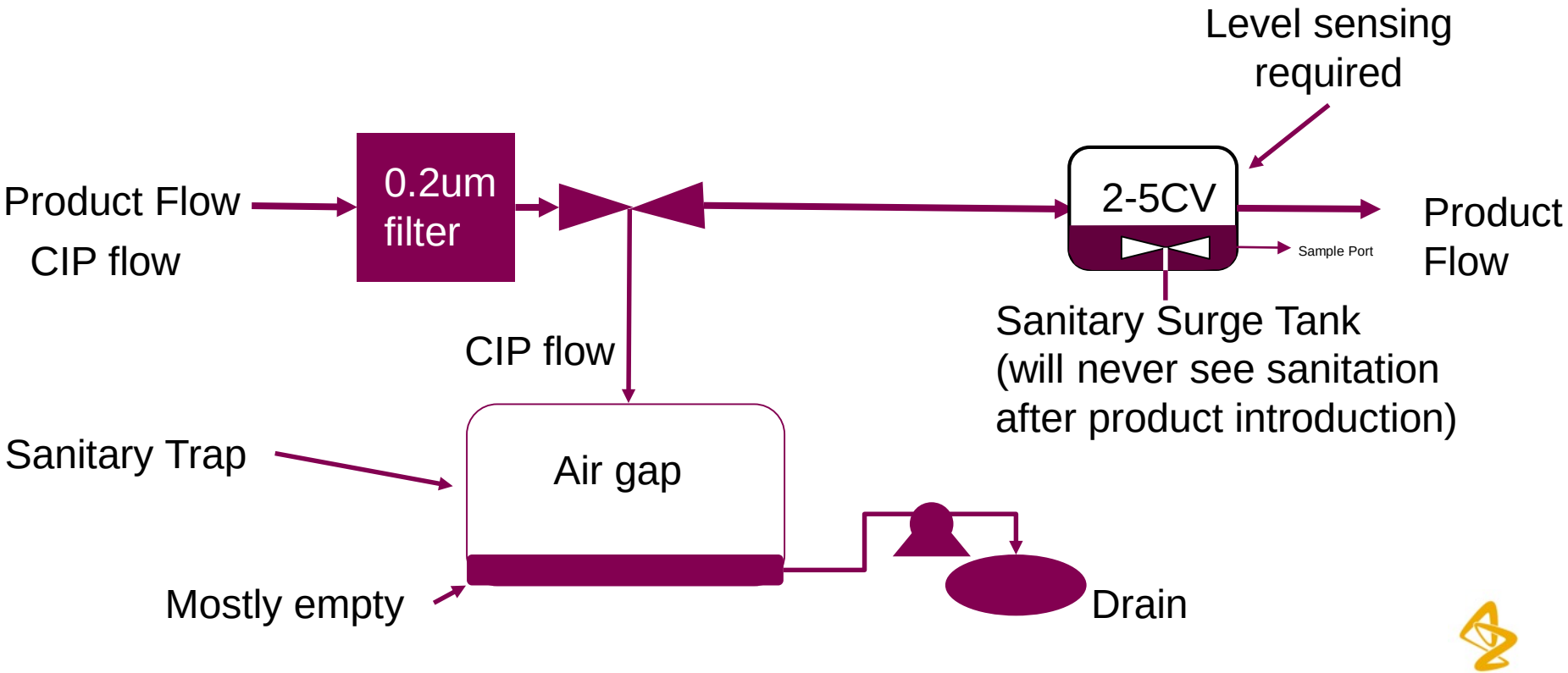
- pH, conductivity, and UV on **inlet** and **outlet** of skid
  - Inlet sensors used for input to Digital Twin for process control
- PAT tools output complex data streams such as spectra
- Complex data analysis, such as machine learning or mechanistic models, supported in GMP environment
  - Need a validation package for complex algorithms

In-line conditioning (IC) needed for buffer prep



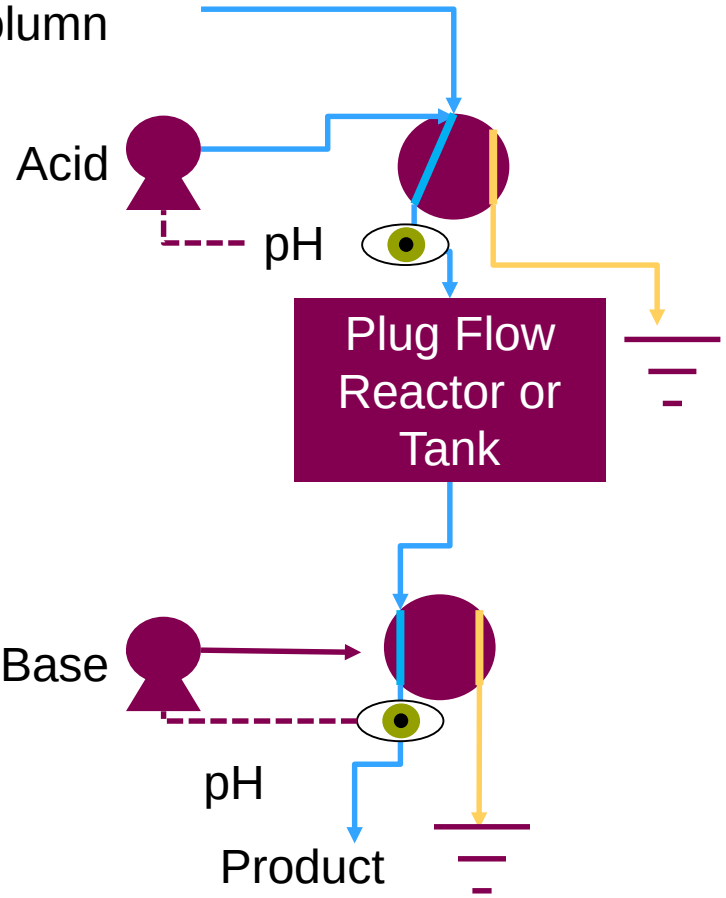
Without IC or buffer dilution,
~2000L buffer/kg produced
Or 100,000L buffer per
50kg batch!

Sanitation fluid and product flow



Virus Inactivation Skid for Batch or Continuous

Cycle time on batch virus inactivation shorter than



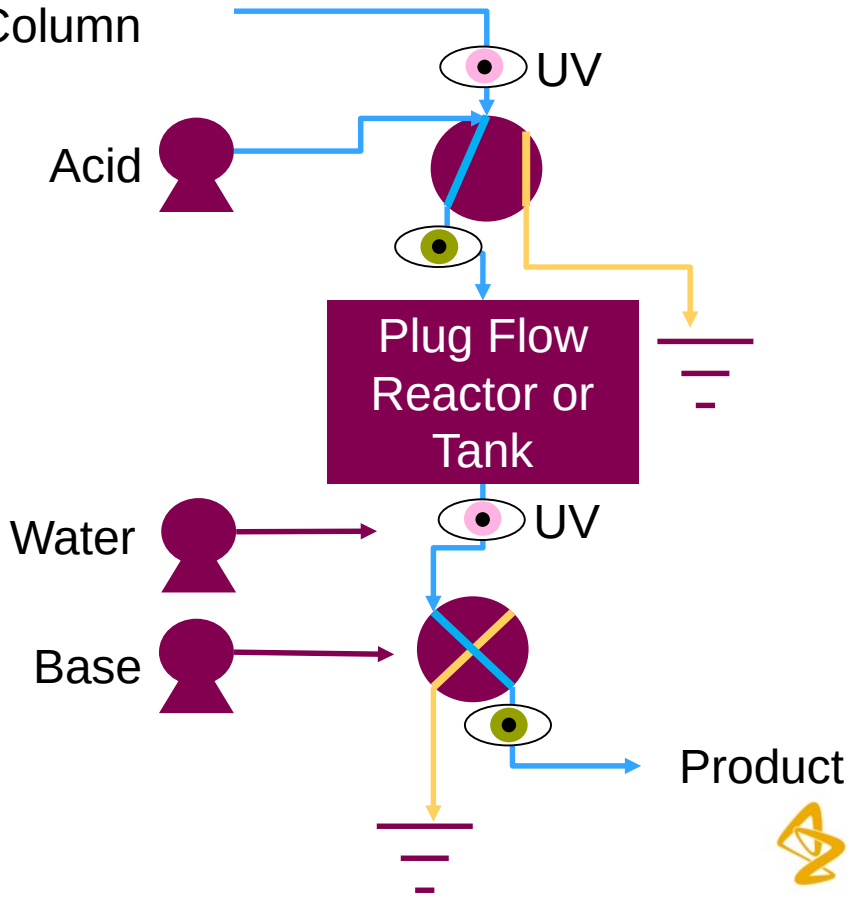
Virus Inactivation Skid for Batch or Continuous

$Q_{acid} \propto UV$

$Q_{base} \propto UV$

$Q_{water} \propto UV$
(to maintain constant ionic strength)

pH



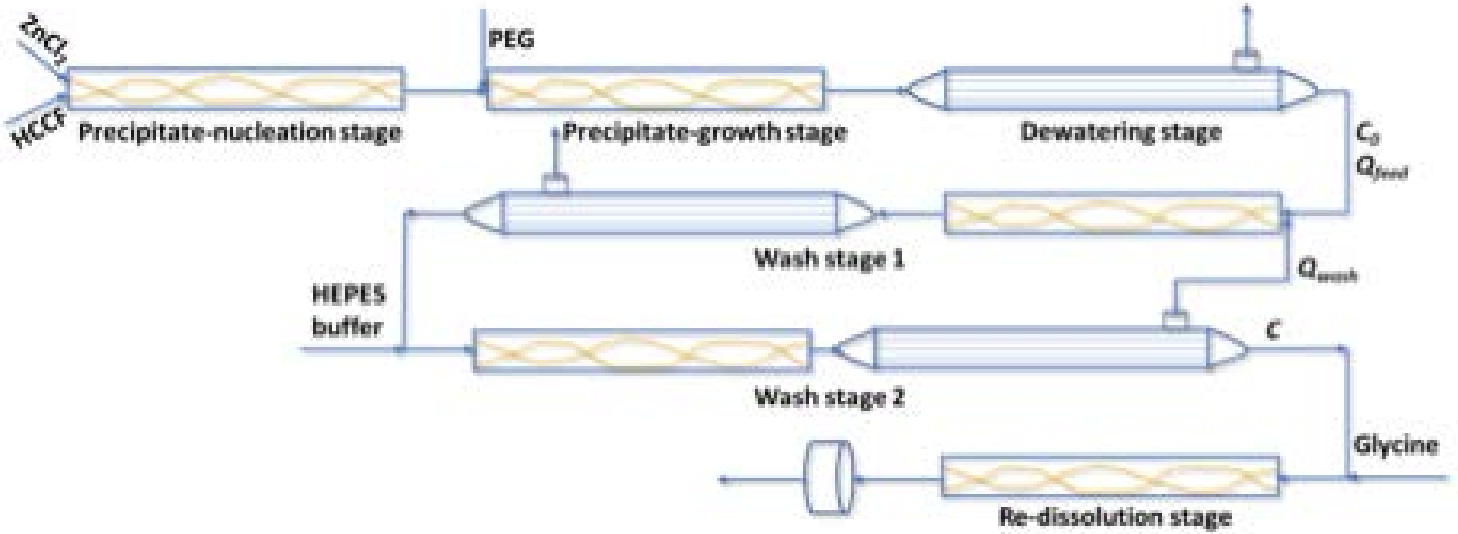
Fault recovery

- Random pressure interlock can happen at any time!
- Peak start failure
- Peak end failure
- Dump cycle to waste
- Virus Inactivation pH excursion
- Buffer OOS
- Load OOS

Other “Next Gen Manufacturing”

- **Membrane adsorbers** downstream would have a total residence time of minutes not hours (FibroSelect from GE, Natrix from Millipore, Gore)
- **Counter current TFF** would be truly continuous without valves or cycling (Przybycien, Coffman, & Zydney)

Precipitation with Counter Current Tangential Flow Filtration



Przybycien, Coffman, & Zydney

Next Generation Manufacturing

- Entry level NGM available to all
- Single Column Chrom skids are capable of upgrading to dual column systems
- Any new purchase of a chrom skid should be at least a dual column set up
- Various trim levels available for all buyers