

# Optimising Multi-Column Protein A Chromatography for Various Manufacturing Scenarios

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Inspired by **patients.**  
Driven by **science.**

# UCB: Inspired by patients. Driven by Science.

Focusing on severe diseases in  
Immunology and the Central Nervous System

- 2015 revenue: €3.9 billion
- ~ 7,800 employees globally
- Operations in 38 countries
- Combining biology & chemistry to make major breakthroughs
- Antibody & small molecules therapeutics
- Partner with the leaders in Pharma
- Active in Biologics arena since 2004 (Celltech-UK acquisition)
- Biologic on the market: Cimzia<sup>®</sup>, a PEGylated anti-TNF Fab' for RA and Crohn's Disease, with new indications
- Innovative Biologic (mAb) currently in Phase 3 includes Romosozumab for Osteoporosis



*Stephanie, living with rheumatoid arthritis*

# Antibody Therapeutics at UCB



*Slough, UK*



*Braine-l'Alleud, Belgium*



- Highly experienced team of scientists
- Industry leading antibody discovery platform
- Many years of experience in antibody engineering
- High-performance mammalian process platform for mAbs
- Industry-leading *E.coli* process platform for periplasmic secretion of Fab'
- Pioneering high concentration liquid formulation
- Facilities across Slough and Braine



# 1. Costs

UCB is evaluating different strategies for the commercial manufacturing of mammalian IgG molecules.

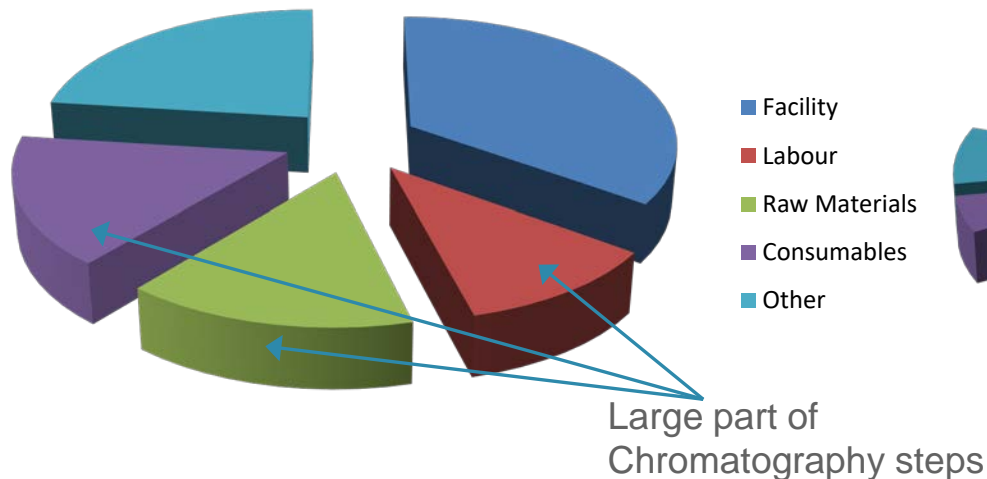
Looking at multi-column chromatography techniques to recommend how we should / shouldn't implement them.

Drug Substance (DS) manufacturing is the biggest cost of COGs

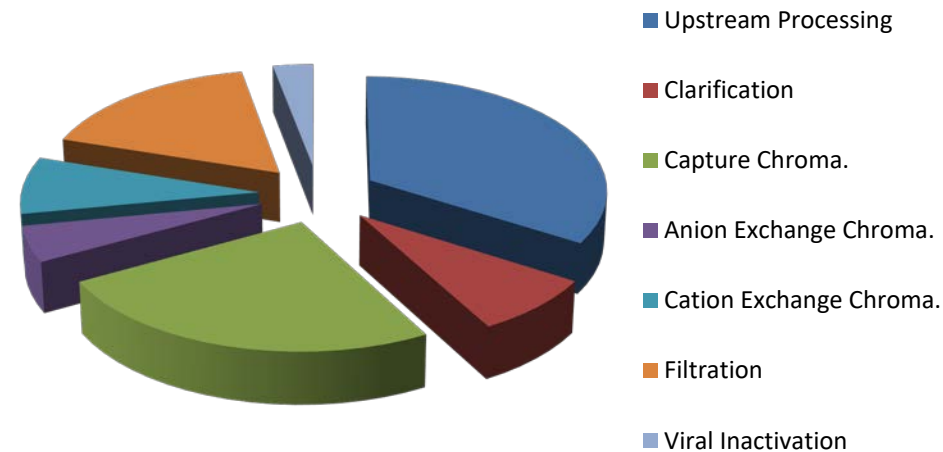
Down Stream Processing (DSP) is the biggest cost of DS manufacturing

Bind & Elute chromatography is the biggest cost of DSP

**Cost Of Goods (COGs)**



**Cost Breakdown of Unit Operations**





## 2. Introduction

### DEFINITION → Continuous purification vs. multi-column chromatography

- 'Continuous' purification is cell culture purified with a continuous flow to drug substance.
- Multi-column (MC) chromatography is running a semi-batch chromatography step with more than 1 inter-linked column.

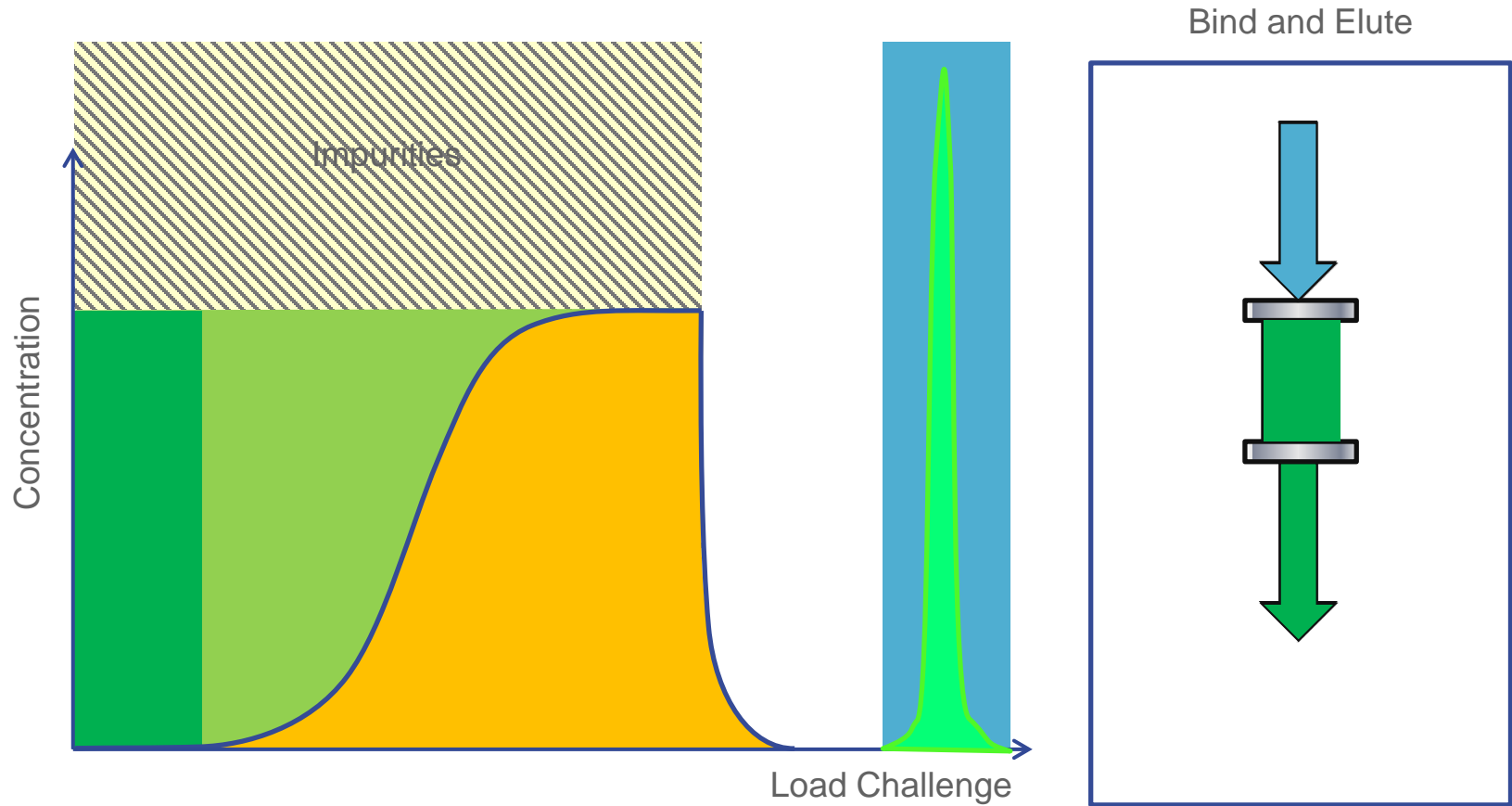
### The potential benefits of multi-column chromatography

- Increase resin utilisation
- Increase productivity
- Decrease buffer consumption
- Reduce manufacturing footprint

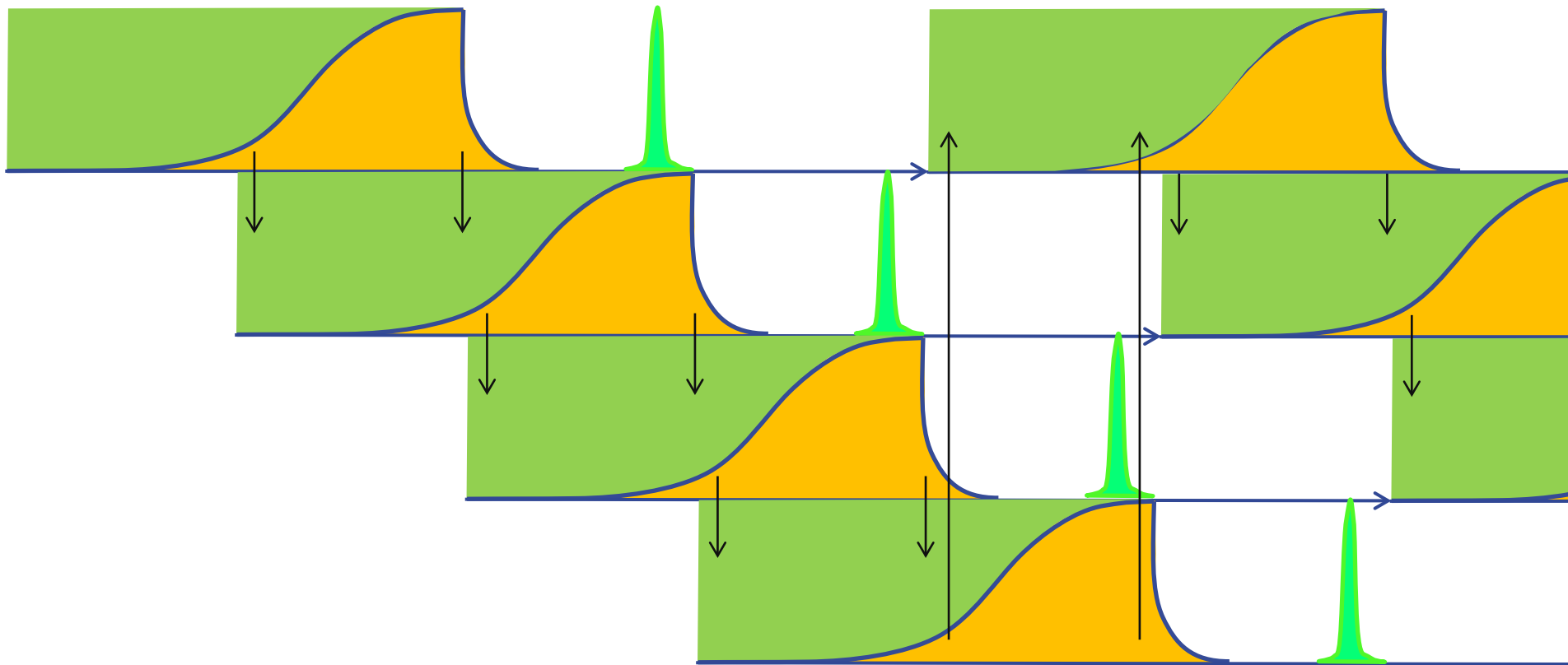
### The drawbacks<sup>\*</sup> of multi-column chromatography

- Increased complexity
- Manufacturing & Regulation
- Needs new hardware system
- Reduced schedule flexibility as difficult to stop between cycles

### 3. Basics of chromatography overloading

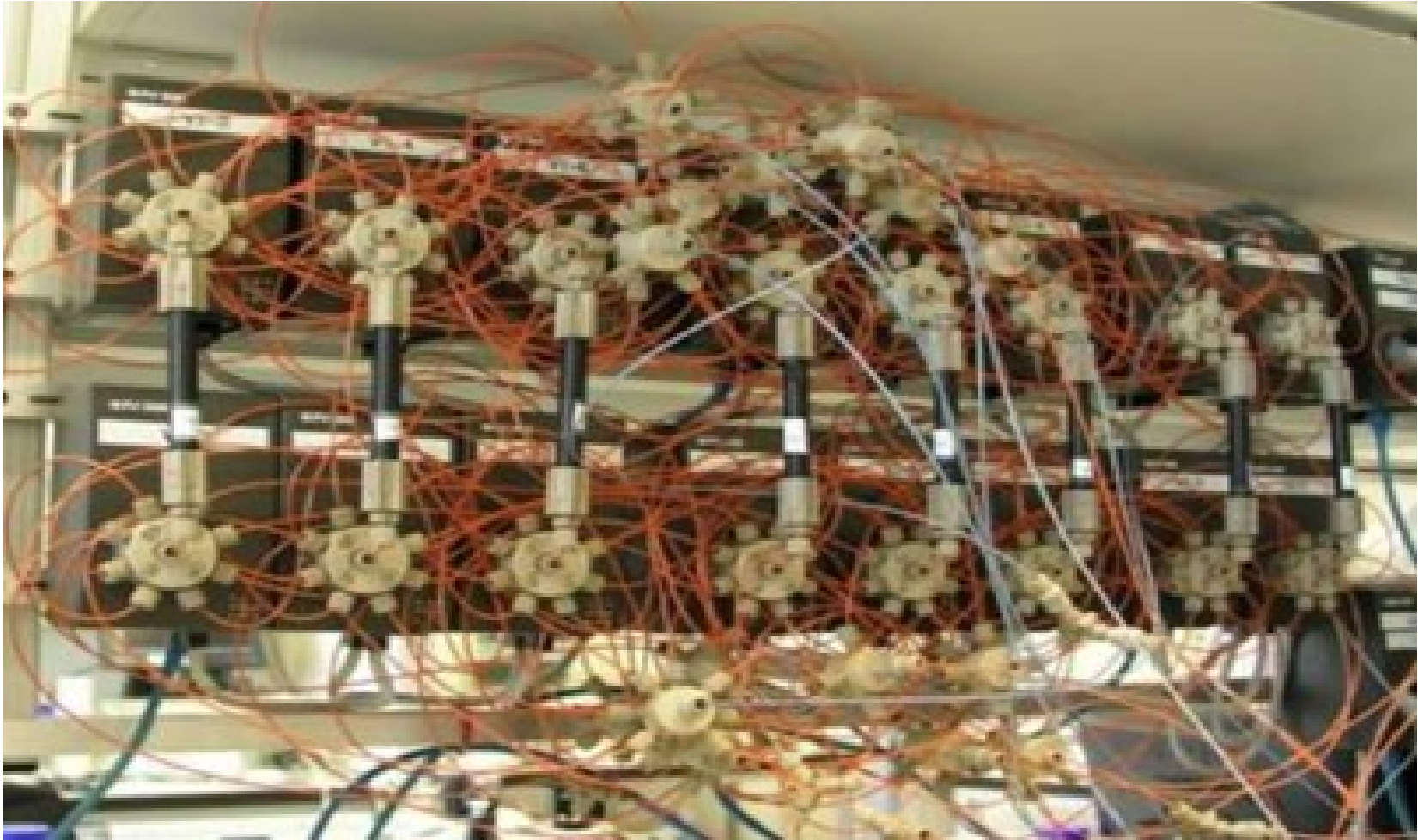


## 4. Multi-column chromatography approaches



# Multi-column chromatography approaches

## The Nightmare



The original 8-column MCSGP system. Morbidelli group: Institute for Chemical and Bioengineering, ETH, Zurich



# 5. Experiments at UCB

## 3-Column-Periodic-Counter-Current

- A MAb-like molecule was evaluated.
- The breakthrough curves for this protein were shallow, so there is even more benefit to use multi-column processes than with IgGs.



	Load Challenge (%)	Residence time (min)	Total Yield (%)	Monomer Yield (%)
Batch	100	8	38	79
PCC Run 1	173	3	39	68
PCC Run 2	173	2	46	80
PCC Run 3	135	2	58	97
PCC Run 4	135	2	64	83

## 6. Experiments at UCB

### 2-Column-Periodic-Counter-Current

- MAb

	Relative load challenge (%)	Residence time (min)	Yield (%)
Batch (3 pilot scale runs)	100	4.8	95
Run 1	100	1.0 (600 cm/h)	94
Run 2	100	0.7 (900 cm/h)	94

- Non-MAb

	Relative load challenge (%)	Residence time (min)	Monomer Yield (%)
Batch	100	8	79
Run 1	280	1 (600 cm/h)	86
Run 2	250	1 (600 cm/h)	91

## 7. Process modelling

The productivity benefit is driven by running at 300cm/h on a 10cm bed height compared to a 20cm bed height in batch mode.

Two different batch processes were modelled against a multi-column process optimised for productivity generated by a equipment provider (3 columns rather than 2):

	Model from supplier (10cm bed height)	Batch (20cm bed height)	Batch (10cm bed height)
Cycle time	1	1.70	1.22
Number of columns	3	1	1
Relative load per period (%)	84	100	100
Load flow rate (cm/h)	337	300	150
All other flow rates (cm/h)	300	300	300
Relative productivity (%)	100.0	69.8 (-30%)	97.3 (-3%)

## 8. Conclusions – Part 1

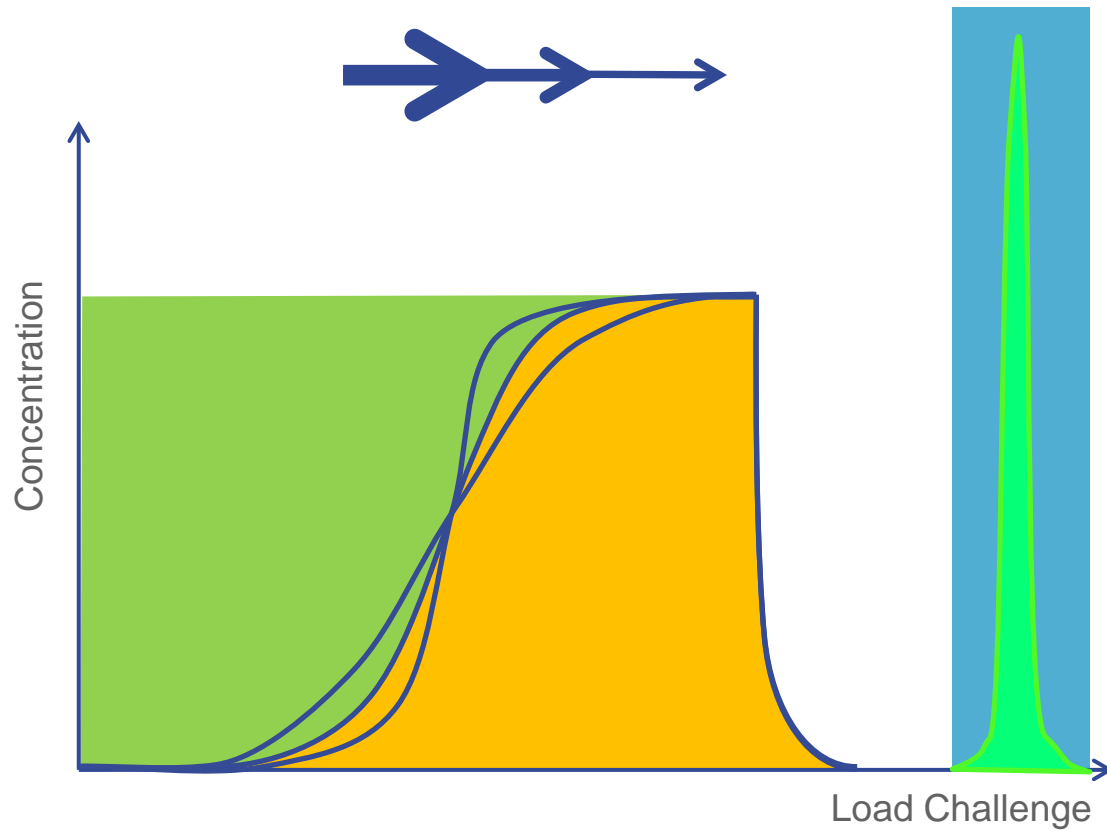
- | Multi-column chromatography increases resin utilisation compared to batch chromatography
- | Multi-column can do great things for purity
- | Multi-column chromatography *appears* to increase the step productivity, however....

- a) The processes are more complicated than batch processes
- b) The scheduling seemed to be slowing things down
- c) There are productivity gains when running the same flow rates on smaller bed heights

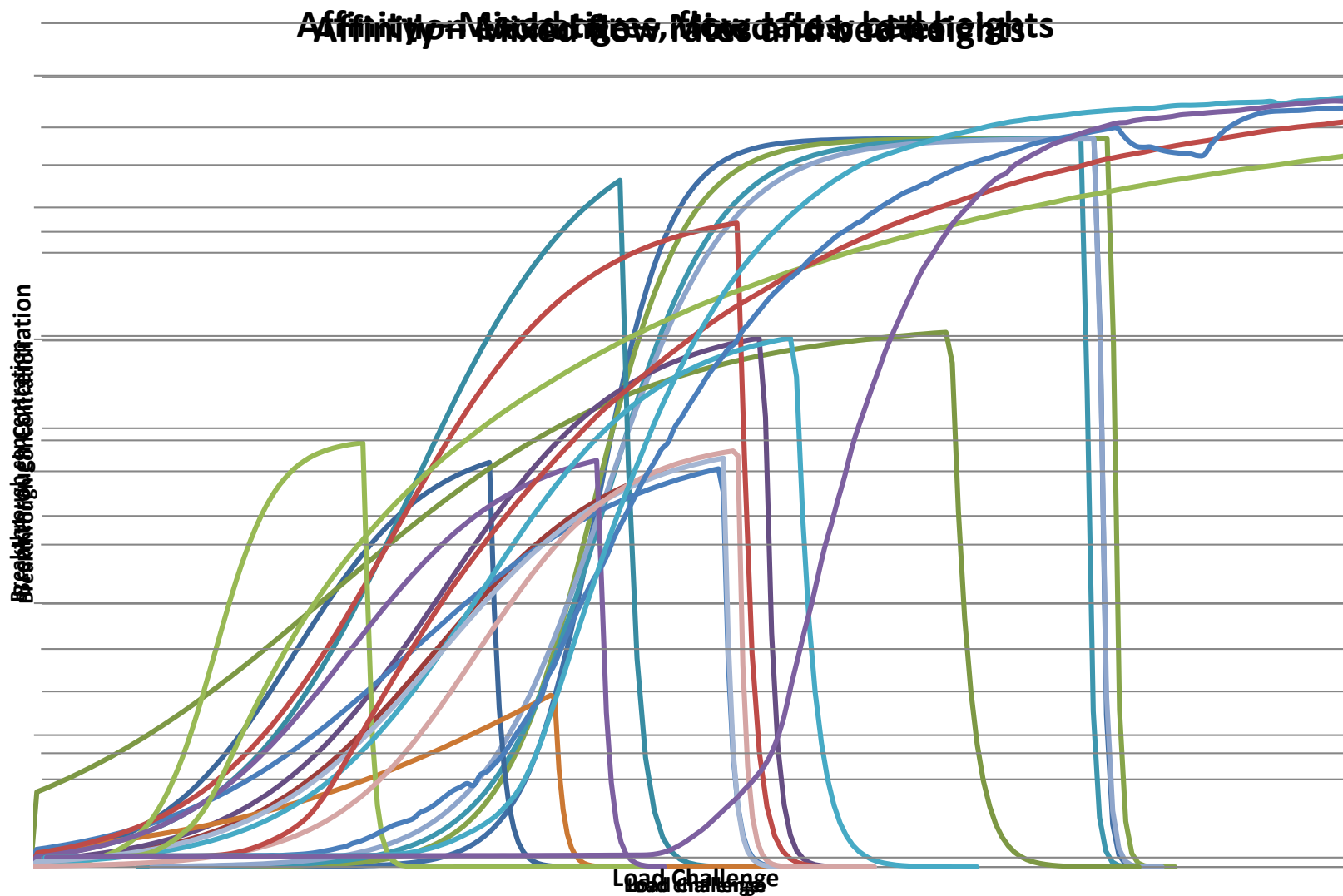
Benefits seen... Challenges seen too

We wanted to understand this better

## 9. Effects of speed

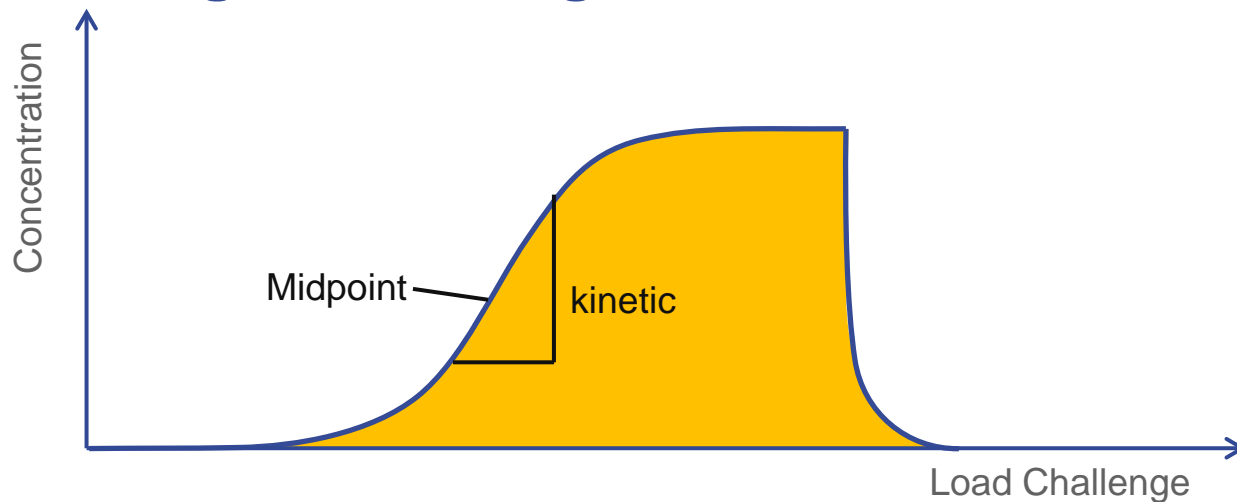


# 10. 'Complete' Breakthrough DBCs

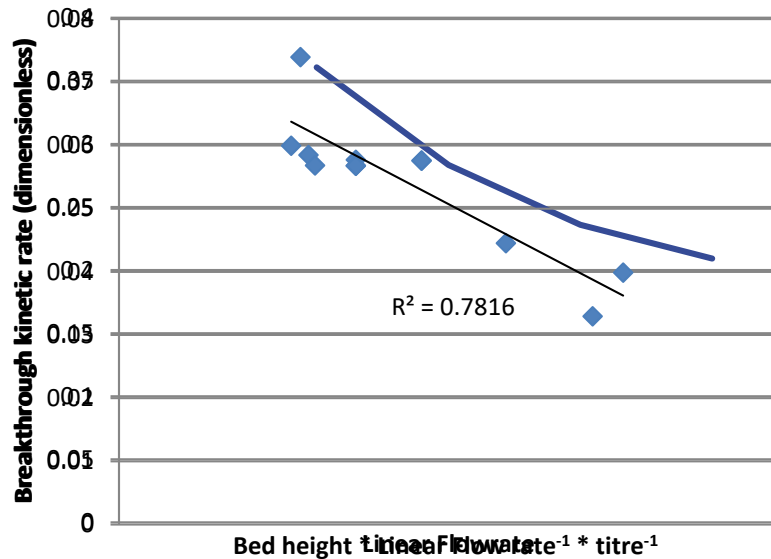




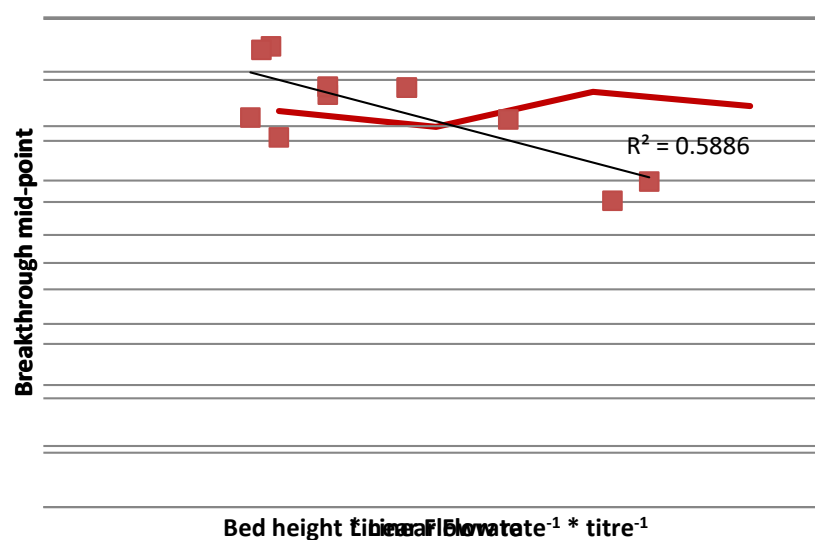
# 10. Breakthrough modelling



Affinity kinetic

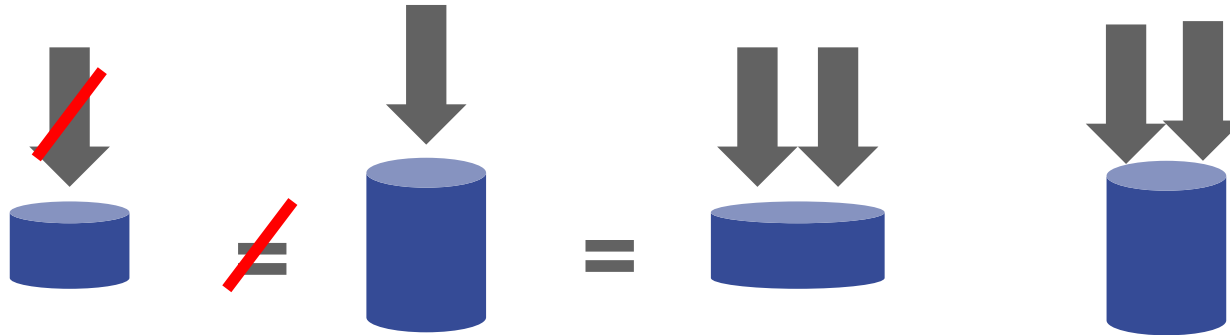


Affinity midpoint (capacity)



# 11. The bed height comparison problem

300cm/h x 10cm bed multicolumn  $\neq$  300cm/h x 20cm bed batch !!!!!



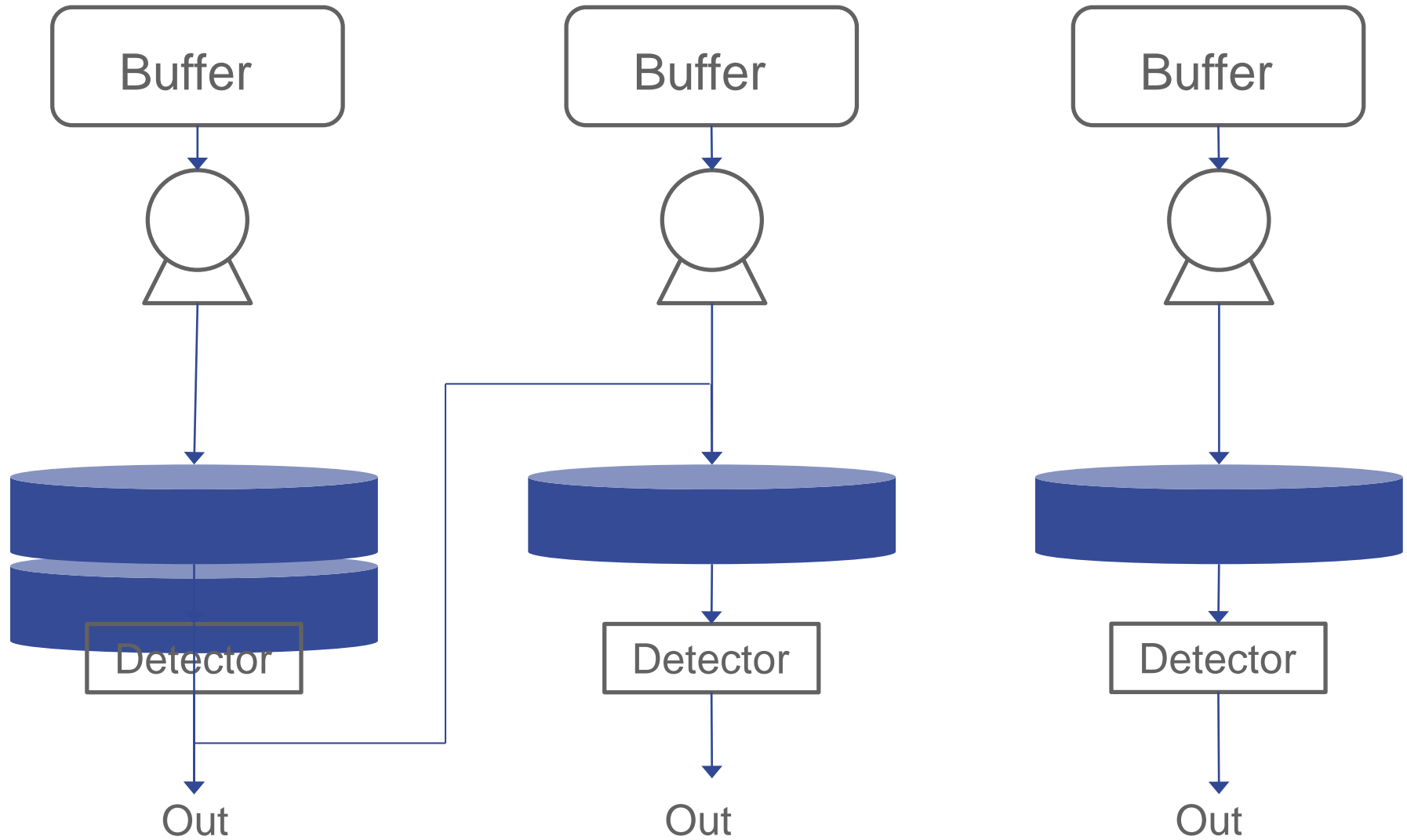
300cm/h x 10cm bed with the same volume (like for like) has double area and therefore double the flow. Therefore product application rate is equivalent to 600cm/h 20cm bed.

On a per volume basis this loads at twice the speed, but we could try loading batch at twice the speed as well. That would be fair.

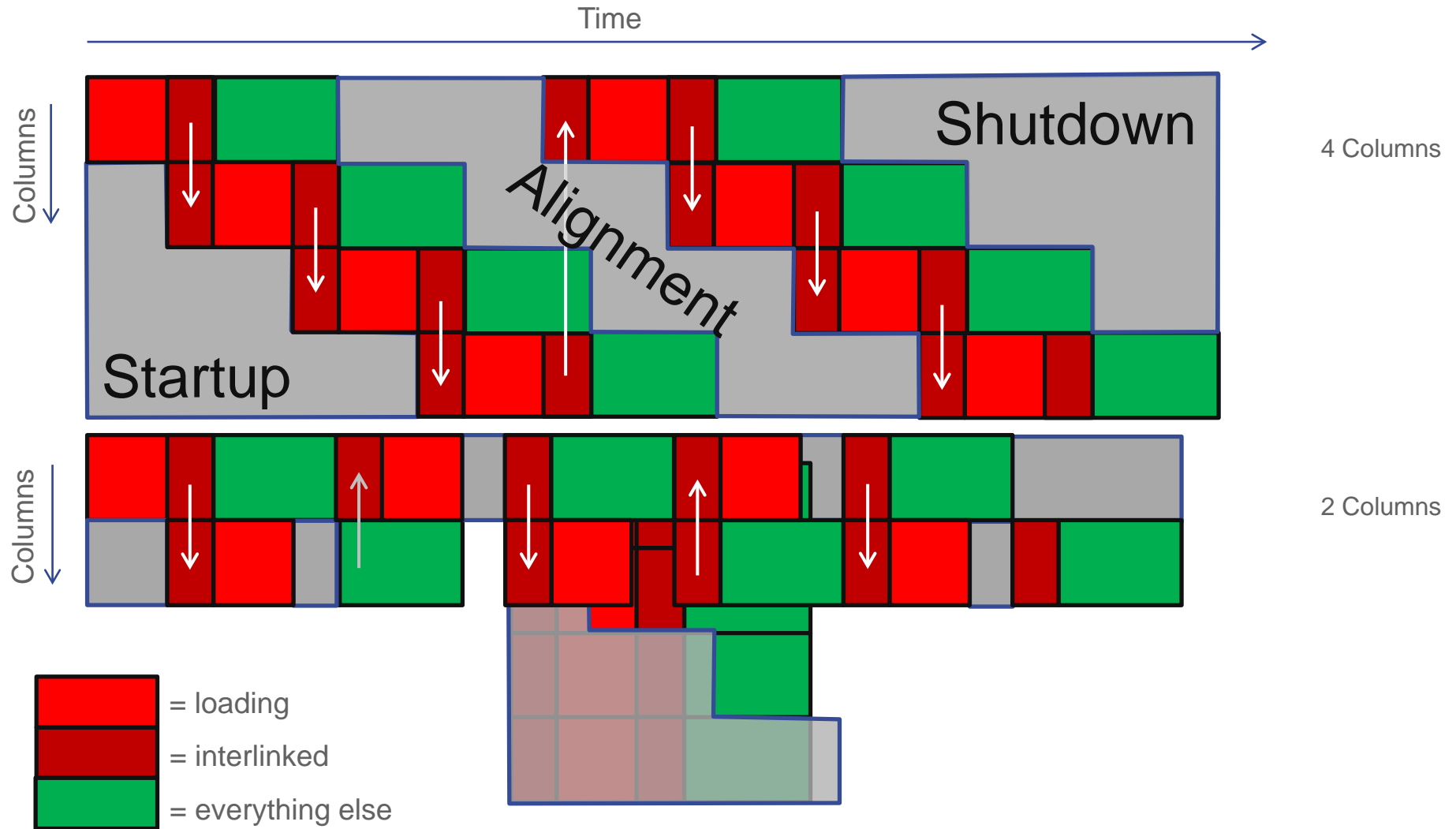
This difference accounts for a lot of the apparent productivity gains of multi-column chromatography

Complicated by multiple columns – all comparisons should be normalised per volume of resin. Per volume basis is ESSENTIAL.

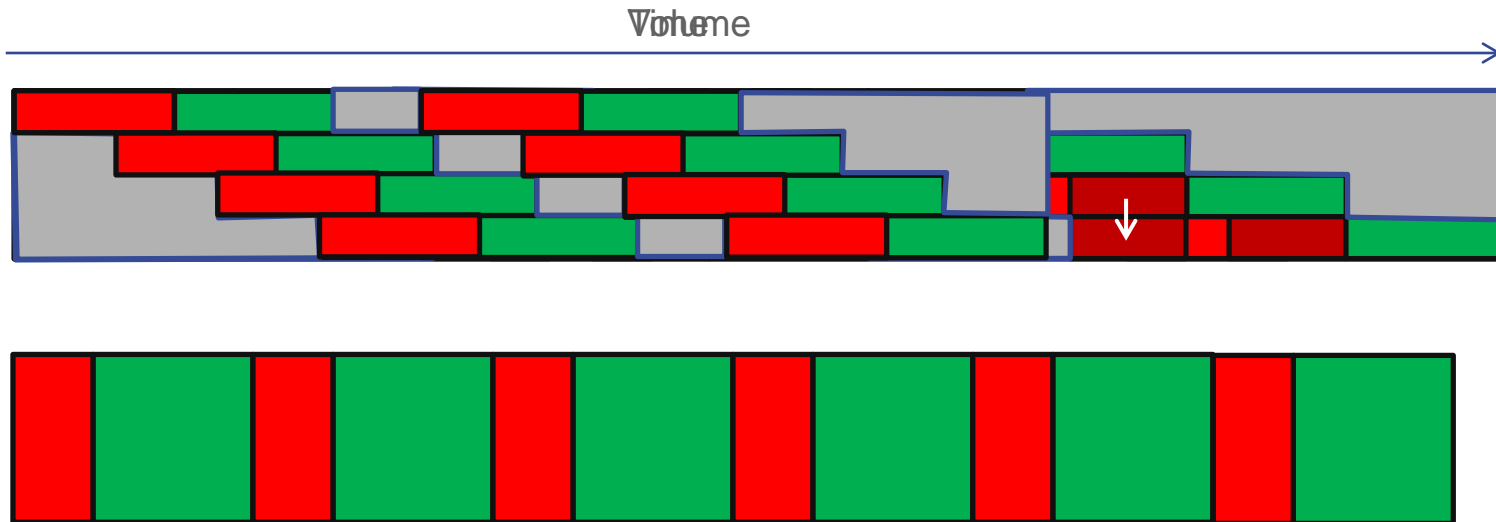
## 12. The Back Pressure Problem



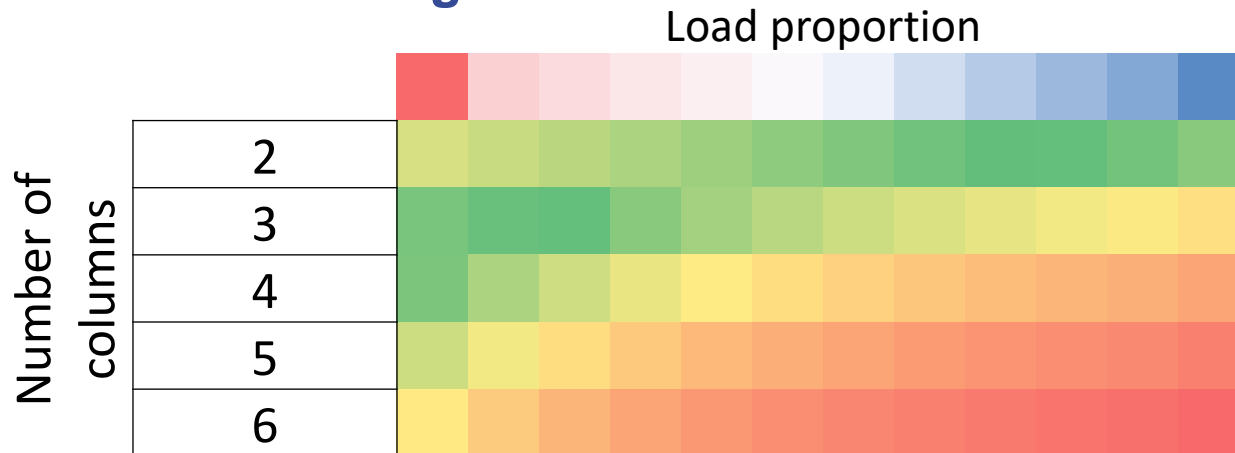
# 13. The scheduling problems part 1



# 14. The scheduling problems part 2



## Alignment Utilisation



# 15. Productivity trade offs

## Dynamic duo

Higher capacity means fewer cycles  
means faster operation

Capacity saturation means  
sustained capacity at higher  
flowrates means faster operation



## The Fatal Five

Higher capacity means more load means longer  
runtime

Interlinked period means some product loads  
through a column twice means longer runtime

Doubled bed height during interlink means  
double back-pressure means halved flowrate

Sequence startup and shutdown means inactive  
columns means dead cycle time

Interlink sequence alignment means hidden  
cumulative dead cycle time





# Is productivity that big a deal?

| Actually, it is.....

## 16. PCC business case

### Scenario:

MAb product in Mammalian host cell

Say a 5g/L titre

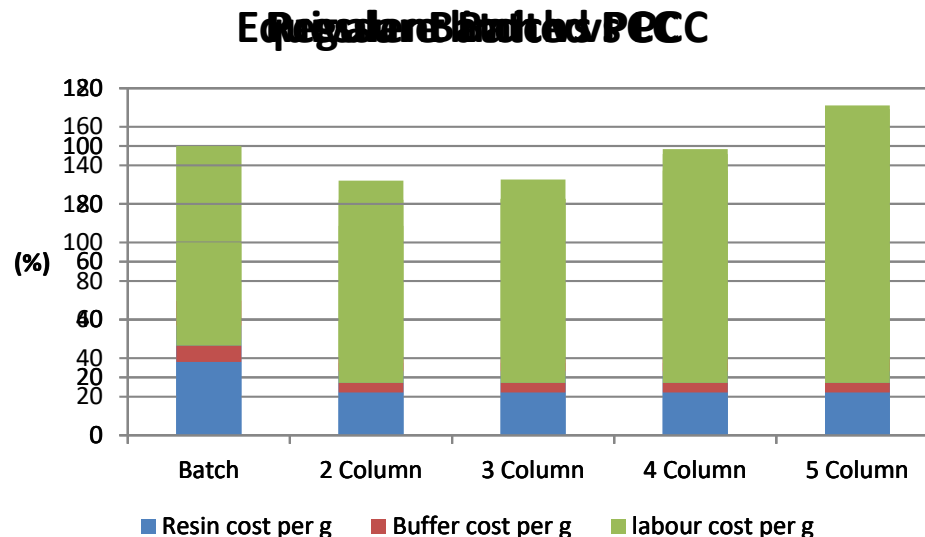
High capacity Protein A capture chromatography step

24/7 facility;

100 cycle lifetime (i.e. all 100 cycles operated in a single run)

### Costs:

Say Labour \$100/h, Buffer \$2/L, Typical cost high capacity Protein A resin



N.B. Mileage may vary

# 17. Practical scenarios

## Pilot/low clinical supply scale

- Demands
  - Few batches
  - High resin cost
  - Long time between batches
  - Short production slots
  - Shift limits
  - High setup overhead

## PCC challenges

- Short campaigns limits cycles that limits PCC utility that limits capacity gain
- Multiple column packs eats cost saving on relatively inexpensive operation
- Short shifts creates multiple start/stop sequences that eat productivity

## High clinical supply/production scale

- Demands
  - Limited buffer storage/floorspace
  - Competitive production slots
  - Productivity heavy cost distribution
  - (High batch value)

## PCC challenges

- Limited productivity often cuts into resin saving
- Multiple Column assemblies take up huge floorspace without all new column arrangement and packing
- Increased complexity and component quantity main raise failure rate with high batch value and productivity effects

## 18. Take home recommendations

- Different manufacturing scenarios require different configurations for multi-column chromatography
- There are complex irreducible schedule effects that you must be careful of
- In general, a 2 column process is usually optimal for capture-step in terms of productivity and process simplicity (*great capacity is par for the course*)
- The capture step is constrained by titre – SPTFF could alleviate this
- There are modalities that give other benefits...if you can make them work
- We can somewhat load balance between capacity and productivity, but holistic cost should be the driver, and the optimal combination is often unexpected.
- This leads to strange results – batch can often be faster and cheaper than MC if you throw away some assumptions
- More columns can actually reduce flexibility rather than increase it.

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# Thanks!



# Questions?

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