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Evaluating facility design and capacity planning decisions for clinical and commercial supply with hybrid continuous processes

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Evaluating Facility Design & Capacity Planning Decisions for Clinical And Commercial Supply with Hybrid Continuous Processes

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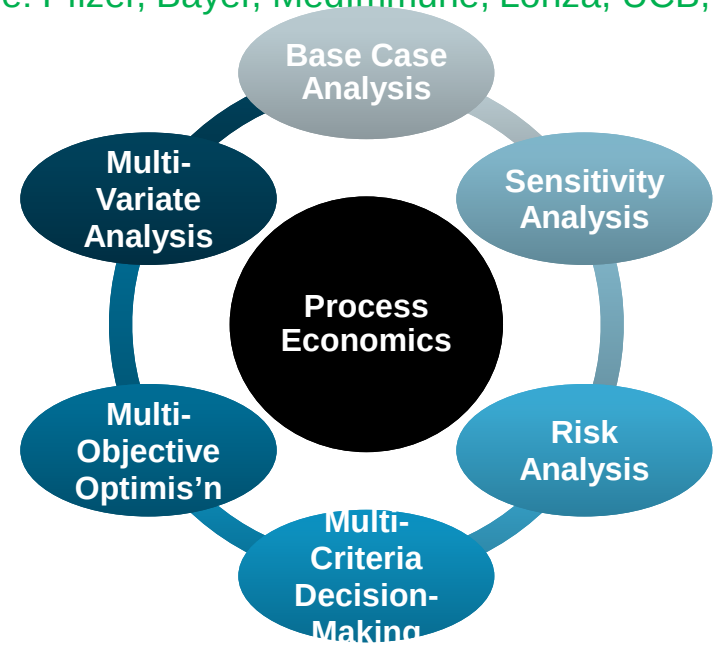
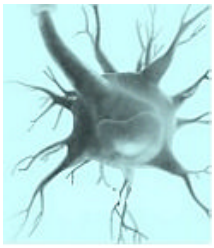
Acknowledgements

	Process Economics: Towards integrated continuous bioprocesses James Pollock, UCL	Facility Optimisation: Continuous & prepacked chromatography Richard Allmendinger, UCL	Capacity Planning: Fed-batch v perfusion portfolios Cyrus Siganporia, UCL
Researcher			
Collaborators & Funding Support	Sa Ho, Pfizer Glen Bolton, ex-Pfizer Jon Coffman, ex-Pfizer	EPSRC Centre user consortium Marc Bisschops, Pall James Rusche, Repligen Karol Lacki, ex-GE	Thomas Daszkowski, Bayer Andreas Schluck, Bayer Soumitra Ghosh, Bayer
PI	Suzanne Farid, UCL Daniel Bracewell, UCL	Suzanne Farid, UCL	Suzanne Farid, UCL Lazaros Papageorgiou, UCL

UCL Decisional Tools – Scope & Approaches

- Systems approach to valuing biotech / cell therapy investment opportunities:
  - **Cost-effective process and facility design**
    - Batch v continuous (Lim et al, 2005 & 2006; Pollock et al, 2013a, 2013b; Farid et al, 2014)
    - Chromatography optimisation (Stonier et al, 2012; Simaria et al, 2012; Allmendinger et al, 2014)
    - SUT for allogeneic cell therapies (Simaria et al, 2014; Hassan et al, 2015)
  - **Capacity planning & Portfolio management**
    - Portfolio management & capacity sourcing (Rajapakse et al, 2006; George & Farid, 2008a,b)
    - Multi-site long term production planning (Lakhdar et al, 2007; Siganporia et al, 2012)
  - **Facility fit**
    - Prediction of suboptimal facility fit upon tech transfer (Stonier et al, 2013; Yang et al, 2014)
- Industrial collaborators include: Pfizer, Bayer, MedImmune, Lonza, UCB, Lilly, Pall, GE, Repligen





Process economics: integrated conti bioprocesses

Researcher

Process Economics: Towards integrated continuous bioprocesses
James Pollock, UCL

Collaborators & Funding Support

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Suzanne Farid, UCL
Daniel Bracewell, UCL

Key questions addressed:

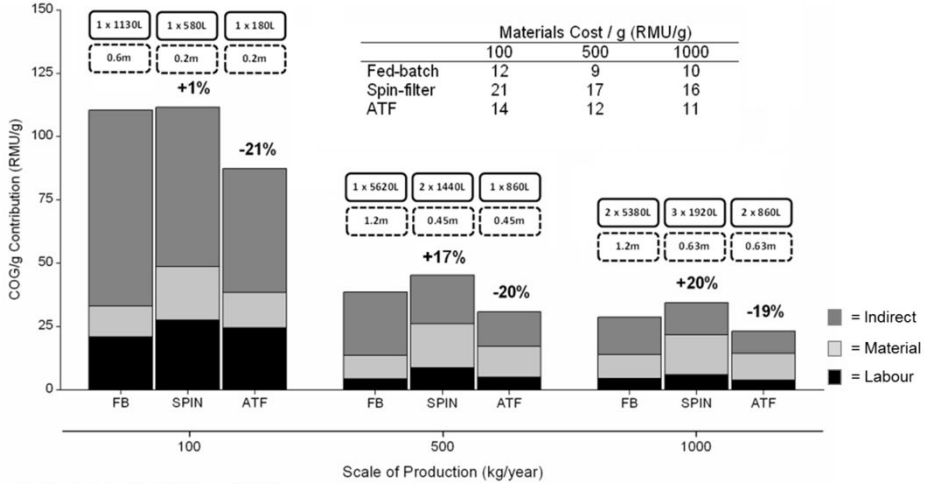
- **Fed-batch versus perfusion systems (Pollock et al, 2013a)**
  - Impact of scale on COG/g?
  - Impact of failures rates on robustness?
- **Continuous chromatography (Pollock et al, 2013b)**
  - Clinical v commercial COG/g?
  - Retrofit costs across devt phases?
- **Integrated continuous processing (Farid et al, 2014)**
  - Impact of development phase, company size and portfolio size on COG/g of ICB?

Process economics: integrated conti bioprocesses

Fed-batch versus perfusion systems (Pollock et al, 2013a)
Continuous chromatography (Pollock et al, 2013b)
Integrated continuous processing (Farid et al, 2014)

Fed-batch versus perfusion culture (New build)

Results: Impact of scale on COG/g for FB v SPIN v ATF processes



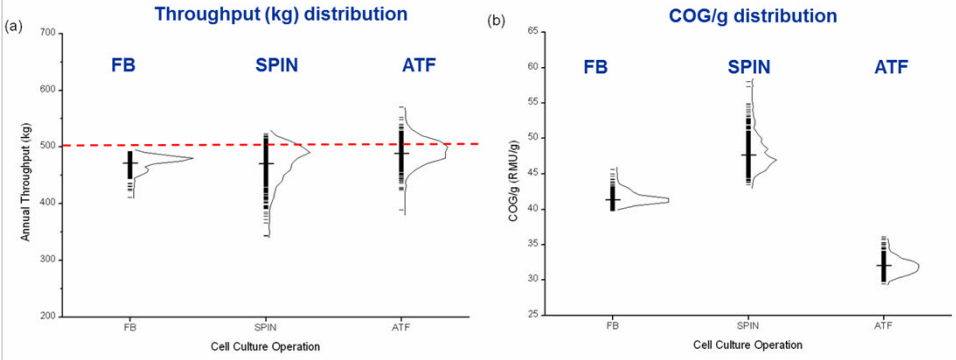
Materials Cost / g (RMU/g)

	100	500	1000
Fed-batch	12	9	10
Spin-filter	21	17	16
ATF	14	12	11

Equivalent fed-batch titre of 5 g/L

Fed-batch versus perfusion culture (New build)

Results: Impact of variability on robustness



Note: 500kg demand, 5g/L titre

Fed-batch versus perfusion – commercial

- ATF Perfusion processes can offer up to 20% COG/g savings
- Cell density for ATF to compete with FB is x3-5–fold higher

- FB – most robust process
- ATF – lowest COG even when accounting for higher variability
- FB and ATF tied if operational and financial benefits weighted equally

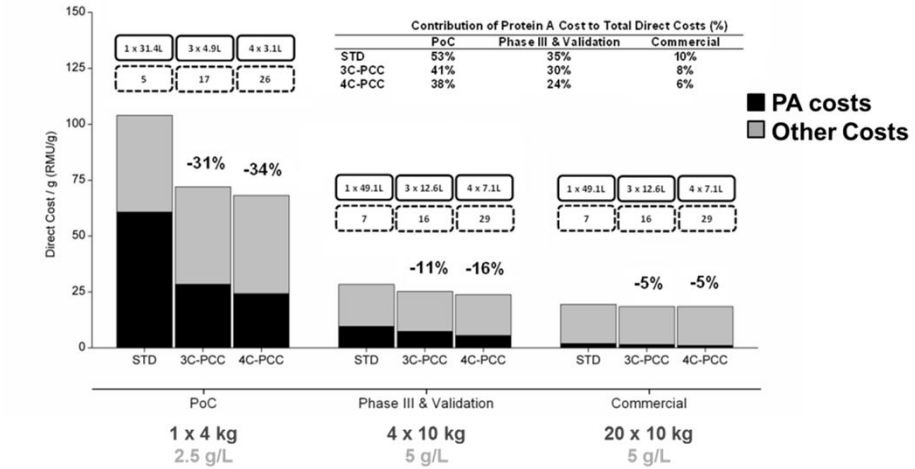
Pollock, Ho & Farid, 2013, Biotech Bioeng, 110(1): 206–219

Process economics: integrated conti bioprocesses

- Fed-batch versus perfusion systems (Pollock et al, 2013a)
- Continuous chromatography (Pollock et al, 2013b)
- Integrated continuous processing (Farid et al, 2014)

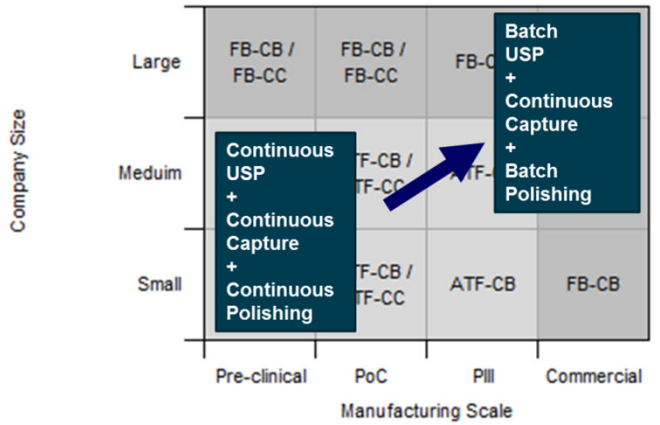
Continuous chrom: clinical & commercial (Retrofit)

Results: Impact of scale on direct costs of standard (STD) v. conti (PCC)



Integrated continuous processes (New build)

Results: Impact of development phase and company size on optimal



Continuous chrom – clinical v commercial

- Continuous chrom offers more significant savings for early phase manufacture
- ~30% COG_{direct} savings @ early clinical v ~5% COG_{direct} savings @ commercial

Pollock, Bolton, Coffman, Ho, Bracewell, Farid, 2013, J Chrom A, 1284: 17-27

Integrated conti processes - multiproduct

- ICB offers savings for smaller portfolio sizes and early phase processes
- Hybrid processes can be more economical for larger / late phase portfolios wrt COG

Farid, Pollock & Ho, 2014, In Subramanian, G. (ed.), Ch 17, pp 433-455.

Facility Optimisation: Conti chrom & prepacked

Researcher

Facility Optimisation: Continuous & prepacked chromatography
Richard Allmendinger, UCL

Collaborators & Funding Support

EPSRC Centre user consortium
Marc Bisschops, Pall
James Rusche, Repligen
Karol Lacki, ex-GE

EPSRC CENTRE for Innovative Manufacturing in Emergent Macromolecular Therapies

PI

Suzanne Farid, UCL

Key questions addressed:

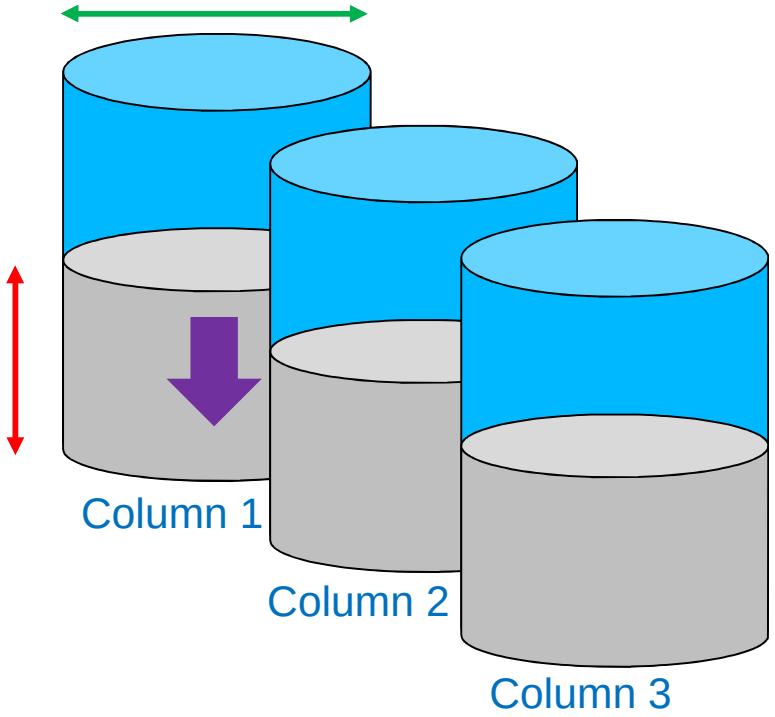
How do the feed characteristics and resin properties impact the **optimal number of columns** to have in a continuous chromatography system?

Does the adoption of **pre-packed disposable** columns change the feasibility of continuous chromatography?

Allmendinger, Farid, in preparation

Facility Optimisation: Conti chrom & prepacked

- Chromatographic parameters to optimize
  - Column diameter
  - Column bed height
  - Loading-linear velocity
  - #Columns



Allmendinger, Farid, in preparation

Facility Optimisation: Conti chrom & prepacked

- Chromatographic parameters to optimize
  - Column diameter
  - Column bed height
  - Loading-linear velocity
  - #Columns
  - Column type: **Self-Packed (SP) Glass vs Pre-packed (PP) Dispo**

PP Dispo

+ Flexibility and ready to use
+ Reduced risk of packing failures
+ Reduced validation efforts
- Limited in size (up to 60cm)
- Pre-packed column costs

Column 1

Column 2

Column 3

Column 1

Column 2

Column 3

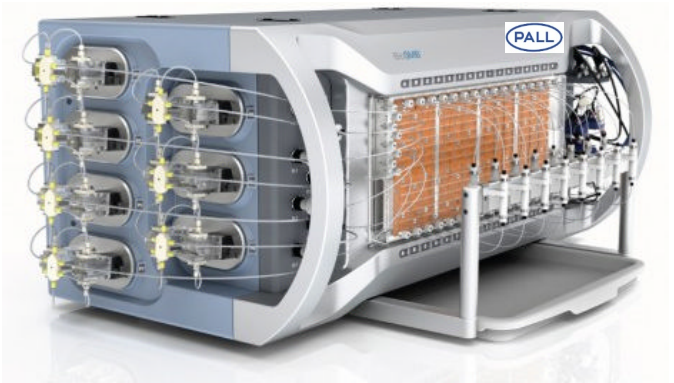
Allmendinger, Farid, in preparation

Facility Optimisation: Conti chrom & prepacked

- Chromatographic parameters to optimize
  - Column diameter
  - Column bed height
  - Loading-linear velocity
  - #Columns
  - Column type: SP Glass vs PP Dispo
  - Chromatography mode: **Batch vs Continuous**

Continuous

+ Improved resin capacity utilization
+ Reduced buffer consumption
- Increased complexity
- High skid price



Allmendinger, Farid, in preparation

Facility Optimisation: Conti chrom & prepacked

- Chromatographic parameters to optimize
  - Column diameter
  - Column bed height
  - Loading-linear velocity
  - #Columns
  - Column type: SP Glass vs PP Dispo
  - Chromatography mode: Batch vs Continuous

- Optimization goal

  Minimize *Cost of Goods = Materials + Labour + Suite + Equipment Depreciation*

Allmendinger, Farid, in preparation

Capacity planning: fed-batch v perfusion portfolios

Researcher

Collaborators & Funding Support

PI

Key questions addressed:

- **Portfolio of labile perfusion products + stable fed-batch products:**
  What is the trade-off between **retrofitting v. CMOs v. new build** to cope with a portfolio of fed-batch and labile perfusion candidates?

- **Portfolio of stable products with option of perfusion or fed-batch processes:**
  How **robust** are fed-batch v. perfusion production plans to **productivity and demand fluctuations**?

Capacity Planning: Fed-batch v perfusion portfolios
Cyrus Siganporia, UCL

Thomas Daszkowski, Bayer
Andreas Schluck, Bayer
Soumitra Ghosh, Bayer

Bayer Technology Services

EPSRC
Engineering and Physical Sciences Research Council

Suzanne Farid, UCL
Lazaros Papageorgiou, UCL

Capacity planning: fed-batch v perfusion portfolios

Project Aims

Multiple products

Multiple facilities

Batch and semi-continuous processes

Questions:

- How best can we use existing capacity in multiple facilities to meet commercial demands?
- Should CMOs or a future facility be considered?
- When and how much capital expenditure is required?

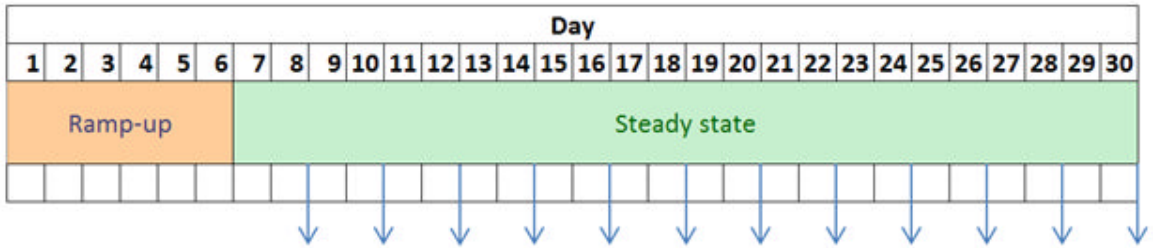
Approach:

- Mixed-integer linear programming
- Minimise total cost

Siganporia, Ghosh, Daskowski, Papageorgiou, & Farid, 2014, Biotechnol Progress. 30 (3), 594–606

Capacity planning: fed-batch v perfusion portfolios

Perfusion scheduling challenges



Culture = 30 days

Harvests

Harvest freq. = 2 days

Freeze harvests

DSP duration = 2 days

Transport

DSP at later date ...or in a different facility

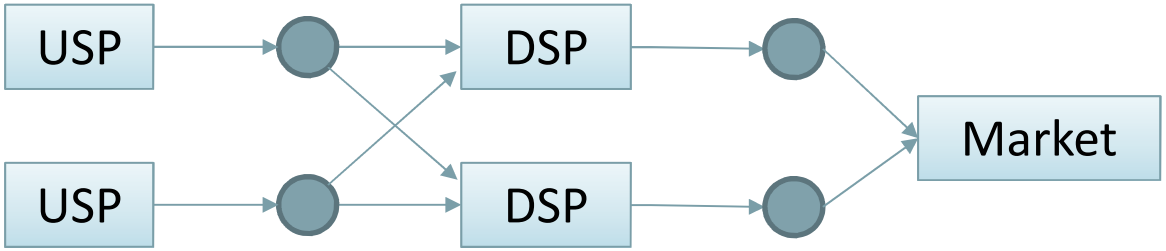
...and perhaps split up

Siganporia, Ghosh, Daskowski, Papageorgiou, & Farid, 2014, Biotechnol Progress. 30 (3), 594–606

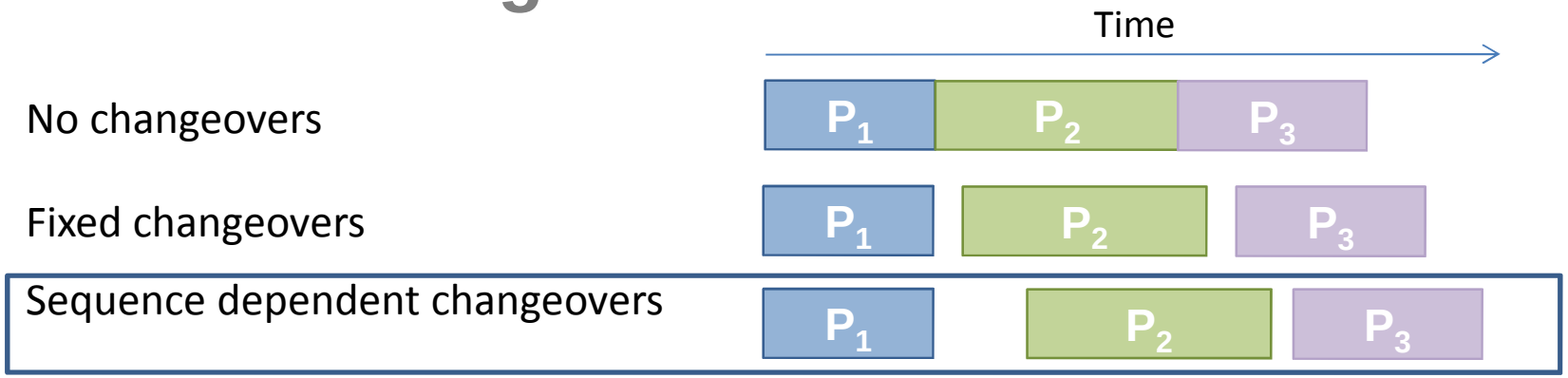
Capacity planning: fed-batch v perfusion portfolios

Perfusion Manufacturing Schematic

Available suites
USP suites: 2
DSP suites: 2



Product Changeovers



Siganporia, Ghosh, Daskowski, Papageorgiou, & Farid, 2014, Biotechnol Progress. 30 (3), 594–606

Capacity planning: fed-batch v perfusion portfolios

Case Study: portfolio of labile and stable products

Problem definition:

Question: Given projected commercial demands over 8 years of 4 products:

- should CMOs, a new build, or retrofitting an existing facility be considered?

- how best should production be allocated across facilities?

PRODUCTS | **OUTPUTS** | **FACILITIES**

$Perf_1$
$Perf_2$
$Perf_3$
FB_1

→

- **Total costs =** Production Cost + Inventory Cost + Investment for future facility + Retrofitting cost + License Fees + CMO Negotiation Costs
- **Capital expenditure**
- **Profit (NPV)**
- **Manufacturing schedule**

←

f_1
f_2
CMO
Future

Siganporia, Ghosh, Daskowski, Papageorgiou, & Farid, 2014, Biotechnol Progress. 30 (3), 594–606

Capacity planning: fed-batch v perfusion portfolios

Case Study: portfolio of labile and stable products

Example of drug-specific data:

Product	Fermentation Mode	Cell Culture Duration	Shelf-life (months)	Annual Demand (AU)					
				1	2	3	…	7	8
$Perf_1$	Perfusion	150 days	24	20	20	20	…	28	30
$Perf_2$	Perfusion	60 days	24	0	0	1	…	10	12
$Perf_3$	Perfusion	28 days	24	0	0	0	…	0.44	0.45
FB_1	Fed-batch	14 days	24	0	0	0	…	3030	3330

Facility capabilities:

Facility	Manufacturing Capability			
	$Perf_1$	$Perf_2$	$Perf_3$	FB_1
f_1	✔ *	✔ *	✔ *	✔ *
f_2	✔	✔ *	✘	✘
CMO	✘	✘	✔	✔
Future	✔	✔	✔	✔

USP scale (max)	
$Perf_1$ - $Perf_3$	FB_1
6 x 200 L	2 x 3000 L

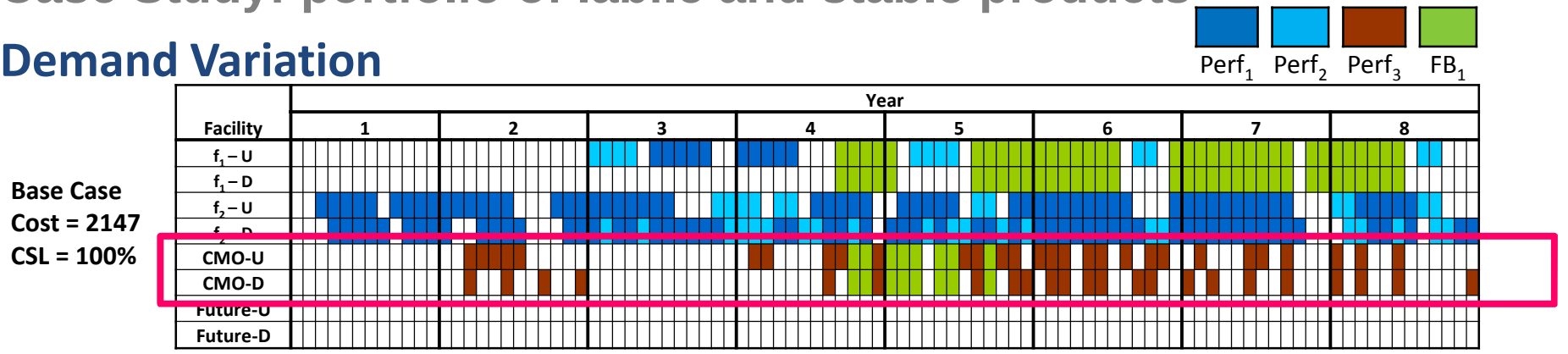
*** Retrofitting is required**

Siganporia, Ghosh, Daskowski, Papageorgiou, & Farid, 2014, Biotechnol Progress. 30 (3), 594–606

Capacity planning: fed-batch v perfusion portfolios

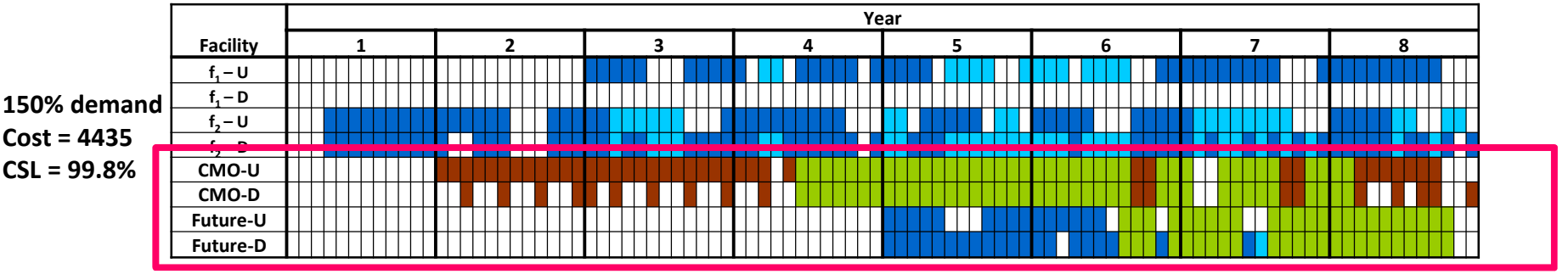
Case Study: portfolio of labile and stable products

Demand Variation



Base Case
Cost = 2147
CSL = 100%

- **Production of $Perf_3$ and any excess demand of FB_1 is outsourced to CMO.**
- **Products are kept within one facility if possible so as to minimise licence fees.**
- **Facility f_1 is not used for the downstream production of products $Perf_1$ and $Perf_2$ to minimise retrofitting.**



150% demand
Cost = 4435
CSL = 99.8%

- **A combination of both a CMO and future build is necessary to meet market demand.**
- **Customer service level drops below 100% in the final year.**
- **Instead of retrofitting f_1's DSP suite, DSP production is carried out in the future build**

Siganporia, Ghosh, Daskowski, Papageorgiou, & Farid, 2014, Biotechnol Progress. 30 (3), 594–606

UCL Decisional Tools Summary

Biotech / Cell therapy company

Therapeutic candidate in early phase development with:

- Early clinical data
  - e.g. cell type, dose estimate, patient numbers
- Early process data
  - e.g. yields

UCL Decisional Tools researchers

UCL Decisional Tools outputs can be used to help with decision-making:

- ❑ Compare the cost-effectiveness of alternative manufacturing processes / supply chains
- ❑ Identify the most **cost-effective** and **GMP-ready** process for
  - *current* scale of operation
  - *future* scales for late phase / commercial manufacture
- ❑ Predict and manage the risk of process changes as products proceed through development pathway
- ❑ Identify most promising technologies and targets to reach for future R&D investment
- ❑ Optimise capacity planning across multi-site multiproduct facilities

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