

# **Up-skilling the next generation of bioprocess engineers**

**Professor Nigel Titchener-Hooker**

# Structure

- Introduction
- Ultra Scale-Down (USD)
- Linking BioSolve to USD
- Outcomes
- What next?

# Ultra Scale-Down

- Tools developed within the IMRC for Bioprocessing
  - Predict how full scale operations may perform
  - Rapid acquisition of data using small amounts of material
  - Early insight into processing issues
- Teaching
  - 1<sup>st</sup> application is in USD of continuous flow centrifugation
  - Approx. 90 students/MBI delegates per year
- Other on-going research programmes looking at
  - Chromatography
  - Filtration
  - Membrane separation

# Examples of IMRC recovery discovery tools



**Shear stress**



**Filtration**



**Centrifugation**



**Chromatography**

also fermentation, cell culture, cell disruption, membrane separations, precipitation, flocculation, freeze drying, formulation .....

# BioSolve

## Process development

### Rapid scenario analysis

- Impact of different titres
- Expression systems (E. coli vs. mammalian)
- Crystallisation vs. Protein A

## Technology assessment

### Analyse the impact of a specific technology within a process

- Disposable bags vs. stainless
- Membrane chromatography
- Perfusion vs. fed batch

## Manufacturing

### First pass analysis

- Facility fit
- Manufacturing scenarios
- Process improvement screening

# Scope

- Link teaching/training with IMRC (Interdisciplinary Manufacturing Research Centre for Bioprocessing) outcomes
  - Undergraduate process design
  - Ultra scale-down (USD) practicals
- Integrate latest industry and IMRC tools:
  - Increase industrial relevance
  - Allow more time for effective teaching
  - Reduce time spent learning how to use software

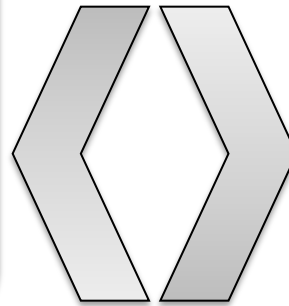
# Knowledge Transfer Secondment



  
**biopharm**

**Industry**

**EPSRC**



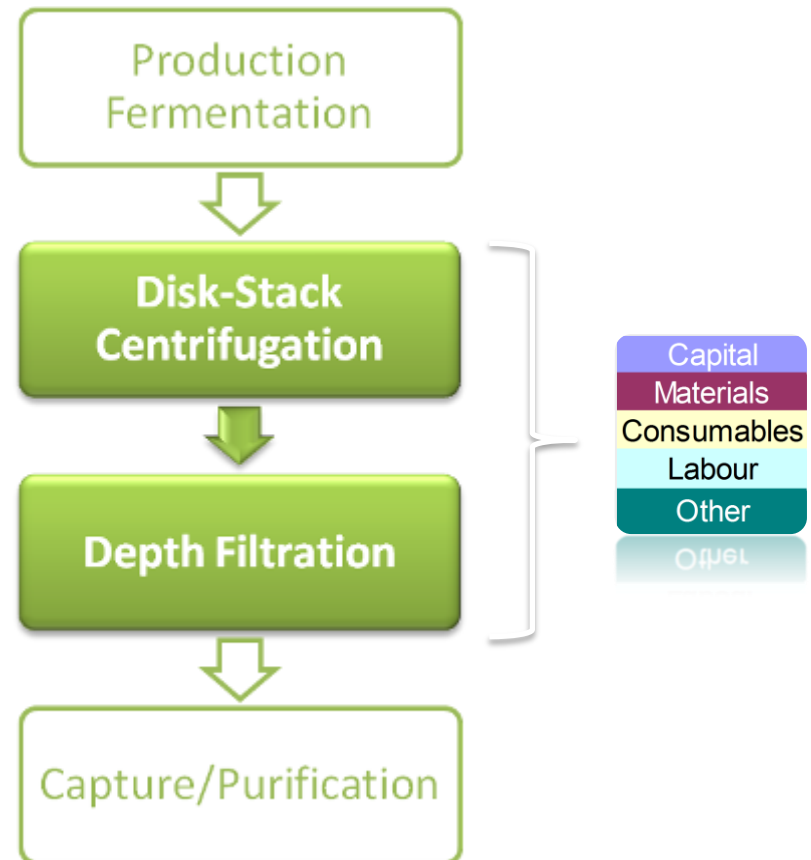
**UCL**

**Academia**

- Bioprocess consultancy
  - Cost modelling specialists
  - Long-term links with UCL
  - Developers of process cost modelling software
- ➔
- Leading centre of excellence in bioprocessing
  - History of close collaboration with industry
  - Developed ultra scale-down methodology

# Centrifugation USD linked model

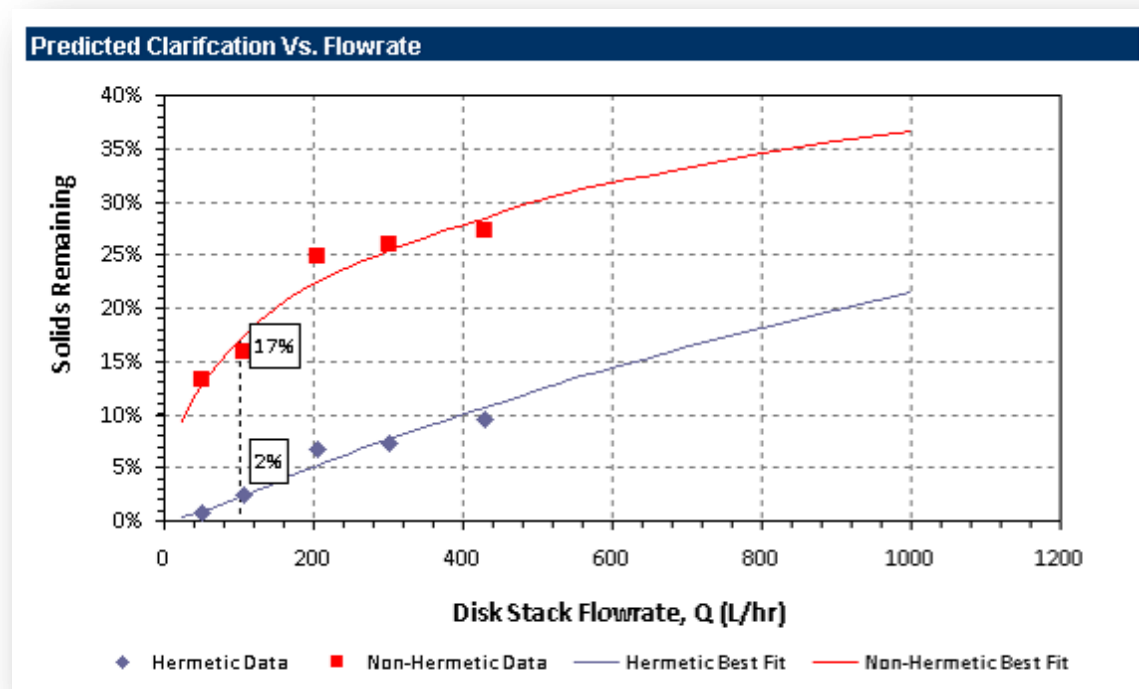
- Model of harvest suite & associated support
- Pilot scale: 100L fermenter
- Centrifuge performance
  - Solids carryover =  $f(\text{rate})$
  - Predicted from USD data
  - Linked to depth filtration
- “High” & “Low” shear centrifuge designs
  - Different costs/processes



# Centrifugation Scenarios

- USD trials
  - Shear device and benchtop centrifuge
  - Mimic shear for different design of feed zone (x2)
  - Mimic a range (x6) of flowrates relative to centrifuge size
- Use of USD results to predict pilot/full scale
- Comparison with industrial centrifuge results
- Translation of USD results into process design and economic appraisal

# USD Predictions



# Process Setup & USD Data

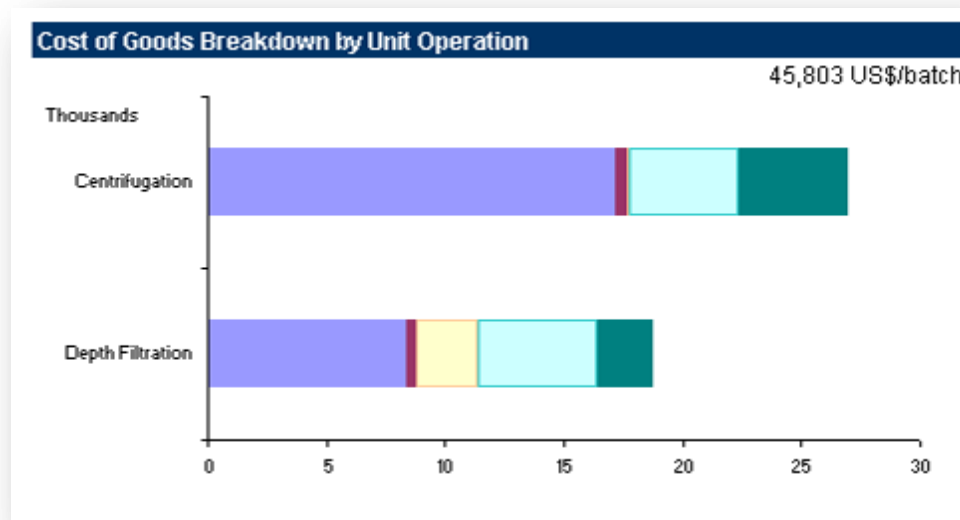
Demonstrator

User

Predicted

Process Definition		Non-Hermetic				
Product Titre (g/L)	2.00	Production Bioreactor Volume (L)	100			
No. Production Bioreactors	1	Target Capacity Utilisation	80%			
Production Bottleneck (hr)	210					
Harvest						
Centrifugation Rate (L/hr)		100				
Depth Filtration Basis:	Loading (L/m <sup>2</sup> )	300	Solids Remaining			
	↳ Predicted	18	↳ Predicted			
Harvest Duration (hr)		5.7	Shift Length (hr)			
			8			
USD Data						
Clarification Results:	No Shear		Sheared@12,000rpm			
	V/tΣ <sub>tab</sub>	Solids Remaining	V/tΣ <sub>tab</sub>	Solids Remaining		
	2.24E-08	0.8%	2.24E-08	13.3%		
	4.69E-08	2.5%	4.69E-08	15.9%		
	8.97E-08	6.8%	8.97E-08	24.9%		
	1.32E-07	7.2%	1.32E-07	25.9%		
	1.88E-07	9.6%	1.88E-07	27.3%		
Large-Scale Σdisk (m <sup>2</sup> )	637					
Process Sequence		Conc (g/L)	Vol (L)	Mass (g)	Yield (%)	Time (h)
Feed		2.00	100	200		
1	Centrifugation	2.00	85	170	85%	9
2	Depth Filtration	1.94	85	165	97%	12

# CoGs Breakdown



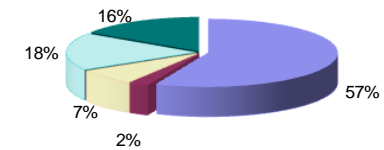
# USD Model Results/Output

- Quick access to results
  - Copy/paste from Excel
  - Output to PowerPoint
- Balanced detail
  - Enough to make results relevant
  - Not too much to swamp user
- Cost summary/breakdowns
- Equipment lists
- Process details
- USD scaling
- Water usage

Equipment: Non-Hermetic

Process Equipment

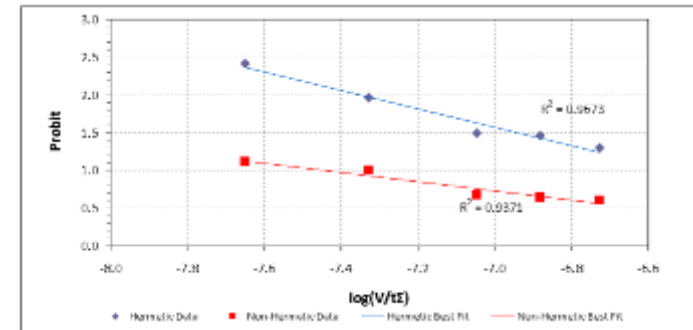
Unit Op	Area	Type	Description	Size	Units	# Used	Factored Cost	Length (m)	Width (m)	Floor Area (m2)	Area Class
1	Recovery	Centrifuge	Non-Hermetic Disk Stack, Centrifuge	100	L/hr	1	96,695	1.4	1.4	2.1	D
1	Recovery	Vessel	Agitator and jacket	100	L	1	28,500	0.5	0.5	0.3	D
2	Recovery	Filter Skid	Filter Skid	6	m2	1	4,946	2.1	0.7	1.4	B
2	Recovery	Vessel	Agitator and jacket	100	L	1	28,500	0.5	0.5	0.3	D
	Buffer Prep	Vessel	Agitator and jacket	500	L	1	37,500	0.8	0.8	0.6	D
	Buffer Prep	Vessel	Agitator and jacket	250	L	1	33,600	0.7	0.7	0.5	D
	Buffer Prep	Vessel	Agitator and jacket	200	L	1	31,500	0.7	0.7	0.5	D



	Gram	Batch	Year	%
Capital	19.44	32,056	961,669	57%
Materials	0.82	1,348	40,446	2%
Consumables	2.57	4,246	127,368	7%
Labour	6.17	10,179	305,383	18%
Other	5.40	8,903	267,081	16%
<b>TOTAL</b>	<b>34.40</b>	<b>56,732</b>	<b>1,701,948</b>	<b>100%</b>

Centrifugation			
Time:	10.5hr	85.0%	Yield
Feed:	1,000L	2.00g/L	
Product:	850L	2.00g/L	

Depth Filtration			
Time:	11.8hr	97.0%	Yield
Feed:	850L	2.00g/L	
Product:	850L	1.94g/L	



# Outputs

Microsoft Excel - BioSolve USD (Centrifugation).xls

File Edit View Insert Format Tools Data Window Help Nitro PDF BioSolve

U52

Process setup

bioSolve

Recalculate PowerPoint

AutoCalc bps

**Process Definition**

Product Titre (g/L)	2.00	Production Bioreactor Volume (L)	100
No. Production Bioreactors	1	Target Capacity Utilisation	80%
Production Bottleneck (hr)	210		

**Harvest**

Centrifugation Rate (L/hr)	100	Solids Remaining	1%
Depth Filtration Basis:		↳ Predicted	17%
Harvest Duration (hr)	5.7	Shift Length (hr)	8

**USD Data**

Clarification Results:

No Shear		Sheared @ 12,000rpm	
WIS <sub>20</sub>	Solids Remaining	WIS <sub>20</sub>	Solids Remaining
2.24E-08	0.8%	2.24E-08	13.3%
4.69E-08	2.5%	4.69E-08	15.9%
8.97E-08	6.8%	8.97E-08	24.9%
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Large-Scale  $\Sigma$ disk (m<sup>2</sup>) 637

**Process Sequence**

	Conc (g/L)	Vol (L)	Mass (g)	Yield (%)	Time (h)
Feed	2.00	100	200		
1 Centrifugation	2.00	85	170	85%	9
2 Depth Filtration	1.94	85	165	97%	12

**Predicted Clarification Vs. Flowrate**

USD predictions

**Cost summary**

	Gram	Batch	Year	%
Capital	154.93	25,549	766,458	56%
Materials	5.73	944	28,331	2%
Consumables	16.16	2,664	79,920	6%
Labour	58.46	9,640	289,212	21%
Other	42.48	7,005	210,162	15%
TOTAL	277.76	45,803	1,374,083	100%

Non-Hermetic 277.8 US\$/g

Total Capital (US\$ M)	Batches per Year	Throughput (kg/yr)	Batch Size (kg)	Yield (%)
3.7	30	4.9	0.2	82%

**CoGs breakdown**

Cost of Goods Breakdown by Unit Operation

45,803 US\$/batch

USD results

USD predictions

Cost summary

CoGs breakdown

# Undergraduate Process Design

## Existing Course

- Intro to bioprocess design
- Techniques
  - Mass/energy balances
  - Equipment sizing
  - Process costing
  - Scheduling
  - Debottlenecking
- The role of simulation
  - Methodologies
  - Strengths/weaknesses

## Objectives of KTS

- Use more relevant data
  - Annual data updates with BioSolve
  - Current industry practices
- Streamline course
  - Reduce time spent teaching software usage
  - Currently multiple workshops
- Increase industrial relevance
  - More projects/case studies
  - Tackle real world issues
- Software
  - Currently SuperPro Designer
  - Replace with BioSolve

# Undergraduate Process Design



## Single-use systems:

- Disposables Vs. Stainless
- Key cost drivers?



## New technologies:

- Chromatography resin
- Trade-offs: Cost, capacity, lifespan



## Location: New build

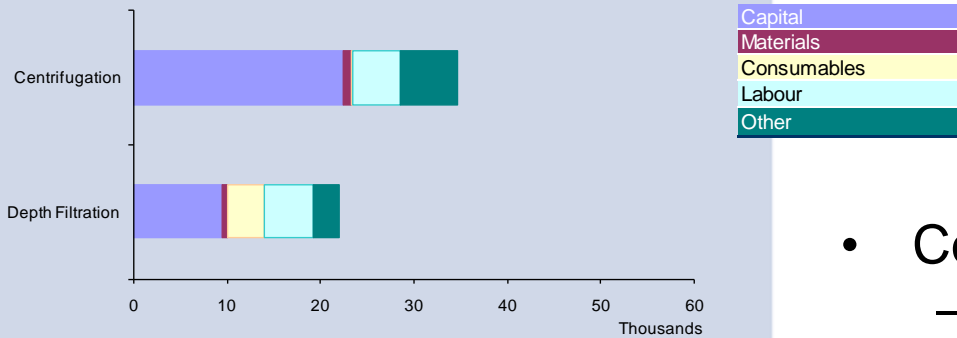
- What if you choose an alternate location?

- Relevant issues
- Quick to implement in BioSolve
- Emphasis on understanding outcomes

# Discussion Points

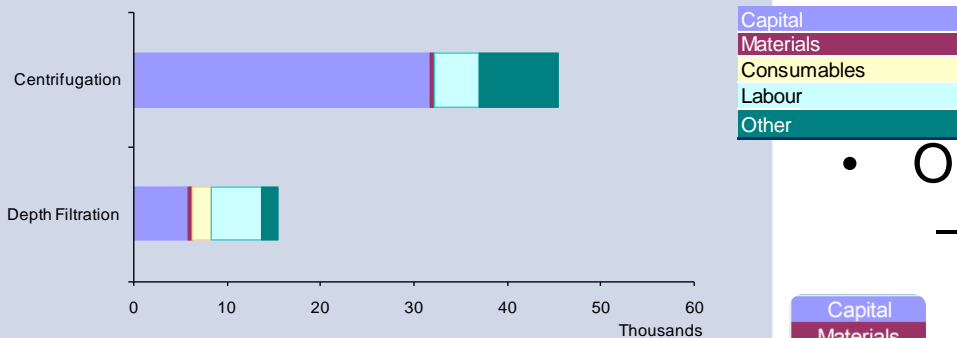
Non-Hermetic

\$57k/batch



Hermetic

\$61k/batch



- Impact of design & operation
  - Depth filtration area required?
  - Overall economics of harvest operations?
- Cost breakdown
  - Largest contributing factor to predicted costs?
  - Proportion of equipment costs relating to support equipment?
  - What could be done to reduce costs?
- Operational constraints
  - What if the harvest operations had to be completed with a single 8hr shift?

# Design Output

In teaching program students look at a industrially relevant project and compete in teams to optimise a process and present the results to a panel. To quote from the wining teams poster in 2011.

“In the current economic climate, cost is emerging as a priority to ensure the success of a commercial product, so considering cost early in process development is crucial. How can a company make decisions on process design and cost targets before committing to capital expenditures? In this project, our team has used BioSolve as a cost and throughput evaluation tool to study the sensitivity of manufacturing production costs and throughput of various process designs and technologies. The aim is to investigate the unit production cost of the antibody IgG to treat arthritis and explore alternatives to the bottleneck steps.”

## Process Optimisation Using BioSolve

Hsiang Chien Hsu, Sofia Labbouz, Moritz Wüstenberg, Chun Ming Yan



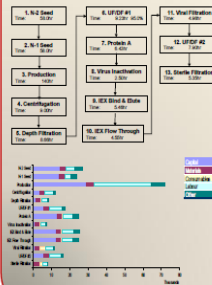
### Abstract

In the current economic climate, cost is emerging as a priority to ensure the success of a commercial product, so considering cost early in process development is crucial. How can a company make decisions on process design and cost targets before committing to capital expenditures? In this project, our team has used BioSolve as a cost and throughput evaluation tool to study the sensitivity of manufacturing production costs and throughput of various process designs and technologies. The aim is to investigate the unit production cost of the antibody IgG to treat arthritis and explore alternatives to the bottleneck steps.



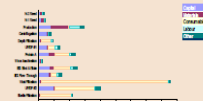
### Process model at pilot scale

A pilot-scale process of 100 L working volume was used as the basis for scale-up.



### Process scale-up to 10,000L (Base-case)

Process scaled-up to 10,000L stainless steel vessel with 80% capacity utilization to meet production demand of 500kg/yr.



### Process Alternatives

- Using disposable systems to reduce FCI and utilities.
- Implementing use of multiple bioreactors to decrease overproduction and minimize the consequences of potential batch failures.
- Increase size of bioreactor to 12,000L and decrease capacity utilization (70%).

### Results of Process Optimisation

- The use of disposable bags enabled to decrease water usage by 230m<sup>3</sup> per batch.



- Using 3x3000L brought the throughput closer to target of 500 kg/year

Size	10,000L	3x3000L
Throughput	579 kg	521 kg

- With 12,000 L bioreactor:

- Product cost decreased by 9.6%
- Annual cost decreased by 6.0%

Base-case scenario					
Costs	Cost	Unit	Value	Unit	%
FCI	1.0	€M	2,110	12,514.01	9%
Energy	2.11	€M	13,276	6,501,913	9%
Consumables	63.26	€M	54,151	27,528,619	89%
LABOR	2.22	€M	95,073	4,278,268	7%
Utilities	1.00	€M	91,762	7,655,165	23%
TOTAL	12.79	€M	1,483,199	6,133,926	100%

12,000L scenario					
Costs	Cost	Unit	Value	Unit	%
FCI	1.46	€M	282,760	12,040,050	19%
Energy	2.36	€M	107,360	5,265,000	10%
Consumables	17.16	€M	80,638	35,472,000	60%
LABOR	1.86	€M	97,175	3,769,019	6%
Utilities	1.46	€M	1,304,024	8,308,418	13%
TOTAL	26.09	€M	1,502,679	6,447,287	100%

### Sensitivity Analysis and Process Debottleneck

Sensitivity analysis carried out for:

- Bioreactor Volume
- Number of Bioreactors
- Product Titer

### Conclusion

- 12,000L vessel with a capacity utilisation of 70% was chosen.
- Viral filtration is by far the most expensive process step
- Replacement of the viral filtration step with a single use membrane chromatography step e.g. Sartobind Q membrane.

Units	Viral Filtration	Sartobind Single Sep Mega
Cost (\$)	490000	10000
Time (h)	4	1.8
Volume (L)	5429	5429
Flowrate (L/h)	905	3000
Concentration (g/L)	2.56	2.56
Capacity (g)	14070	10900
Requirement (pcs)	1	1.5
Total Cost (\$)	490000	22500
Reduction		94.5%

- Overall cost reduction is 26.7%
- This change could replace steps 10 and 11, time requirement reduced by 7.7 hours
- BioSolve useful tool to identify bottlenecks and alternative manufacturing strategies

# Conclusions

- Demonstrated the value of academic industrial collaboration
- Valuable insights from linking BioSolve process models to directly to outputs from USD experiments
  - Potential applications in process development
- Has value in supporting teaching programmes
- Linking USD to BioSolve for the whole process has potential to
  - Support process selection early on in development
  - Help speed the development of cheaper robust processes

# Future

- Adapt the same approach for other operations
  - TFF
  - UF
  - Chromatography
- Expand scenarios
  - Combine USD models
  - Process comparisons
  - Impact of uncertainty

## Acknowledgements:

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