Up-skilling the next generation of bioprocess engineers

Professor Nigel Titchener-Hooker

Structure

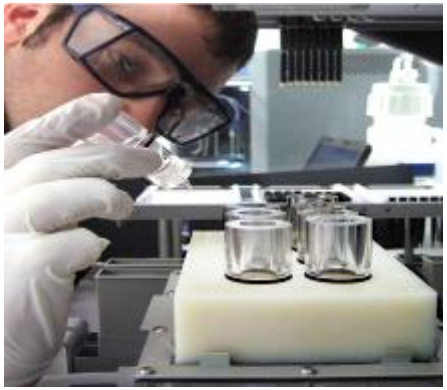
- Introduction
- Ultra Scale-Down (USD)
- Linking BioSolve to USD
- Outcomes
- What next?

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
  - 1st 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

EPSRC

biopharm

Industry

UCL

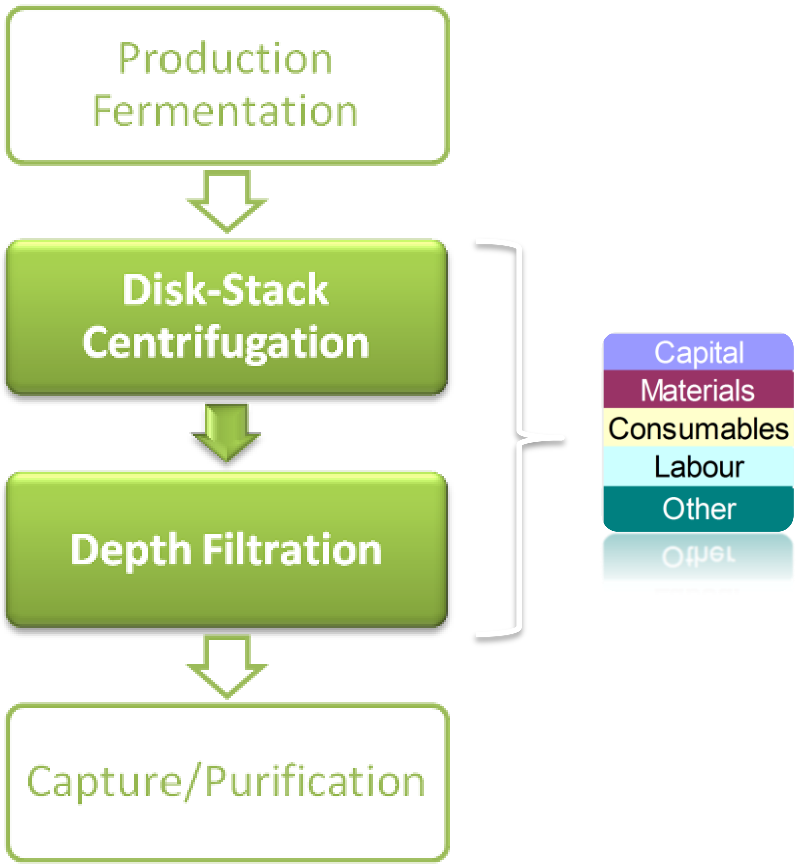
Academia

- 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

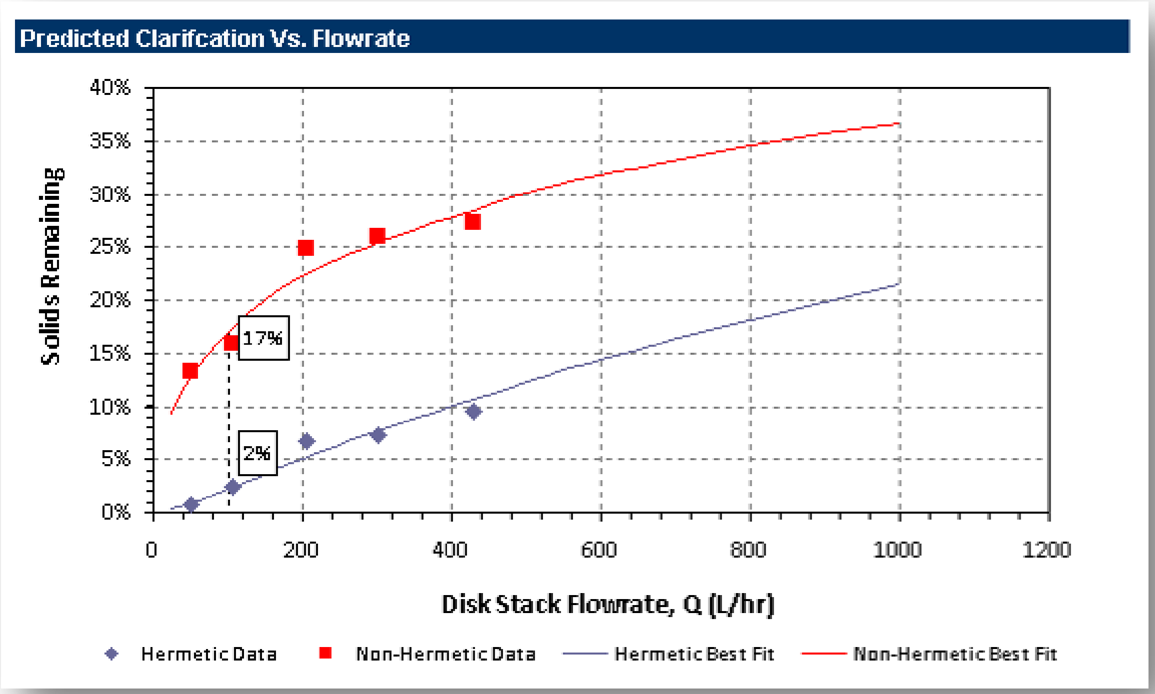
- Model of harvest suite & associated support
- Pilot scale: 100L fermenter
- Centrifuge performance
  - Solids carryover = f(rate)
  - Predicted from USD data
  - Linked to depth filtration
- "High" & "Low" shear centrifuge designs
  - Different costs/processes



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

bioSolve

Recalculate PowerPoint

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/m²)	300	Solids Remaining	1%
	↳Predicted	18	↳Predicted	17%
Harvest Duration (hr)		5.7	Shift Length (hr)	8

USD Data

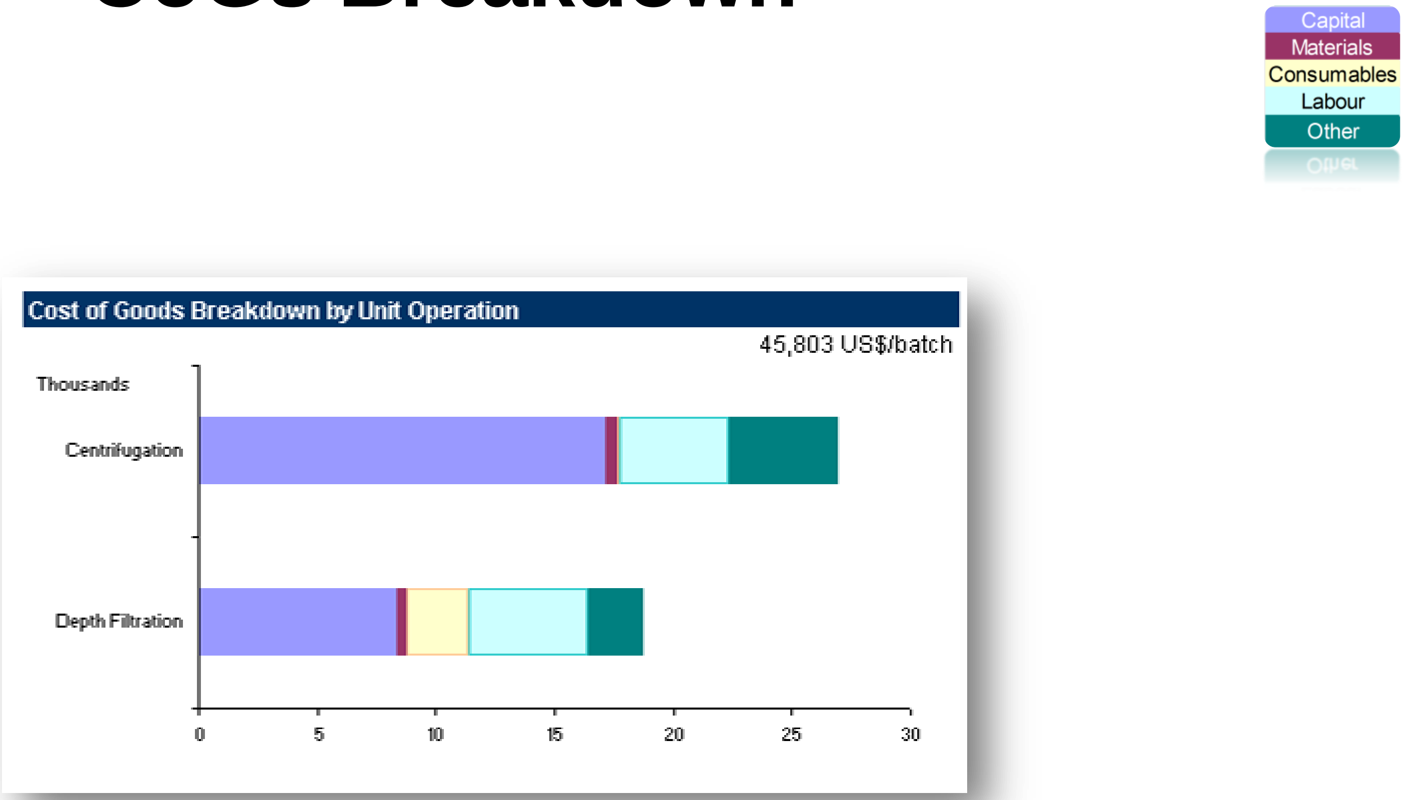
Clarification Results:

No Shear $V/t\Sigma_{lab}$	No Shear Solids Remaining	Sheared@12,000rpm $V/t\Sigma_{lab}$	Sheared@12,000rpm 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 (m²): 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



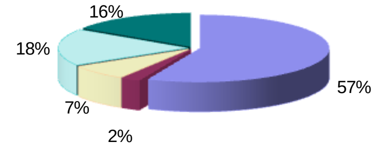
USD Model Results/Output

- 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

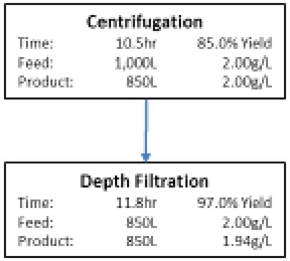
Equipment: Non-Hermetic

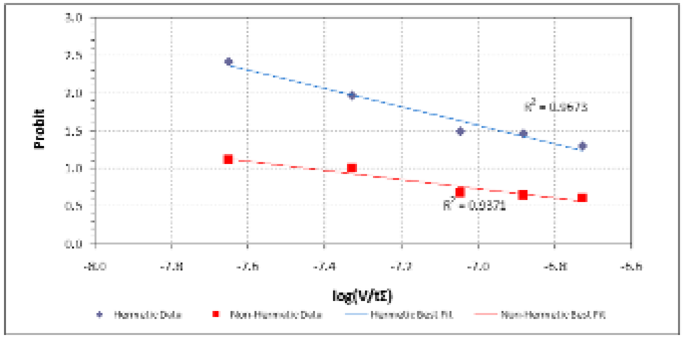
Process Equipment

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

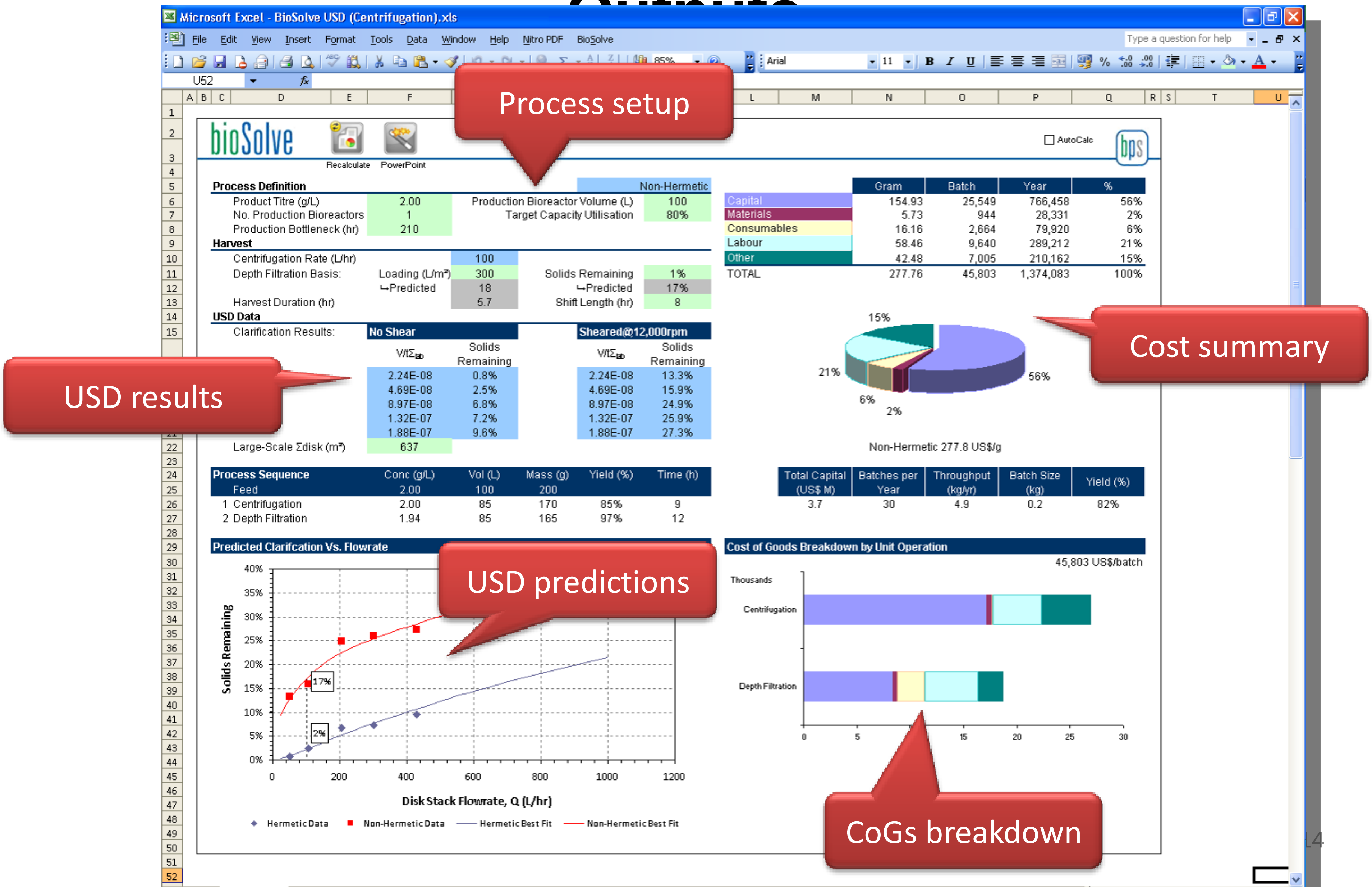


	Gram	Batch	Year	%
Capital	19.44	32,056	961,669	57%
Materials	0.82	1,348	40,446	2%
Consumables	2.57	4,246	127,368	7%
Labour	6.17	10,179	305,383	18%
Other	5.40	8,903	267,081	16%
TOTAL	34.40	56,732	1,701,948	100%





Outputs



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/m²)	300	Solids Remaining		1%
	↳Predicted	18	↳Predicted		17%
Harvest Duration (hr)		5.7	Shift Length (hr)		8

USD Data

Clarification Results:	No Shear		Sheared@12,000rpm	
	$V/t\Sigma_{ds}$	Solids Remaining	$V/t\Sigma_{ds}$	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 (m²) 637

	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%

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

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

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

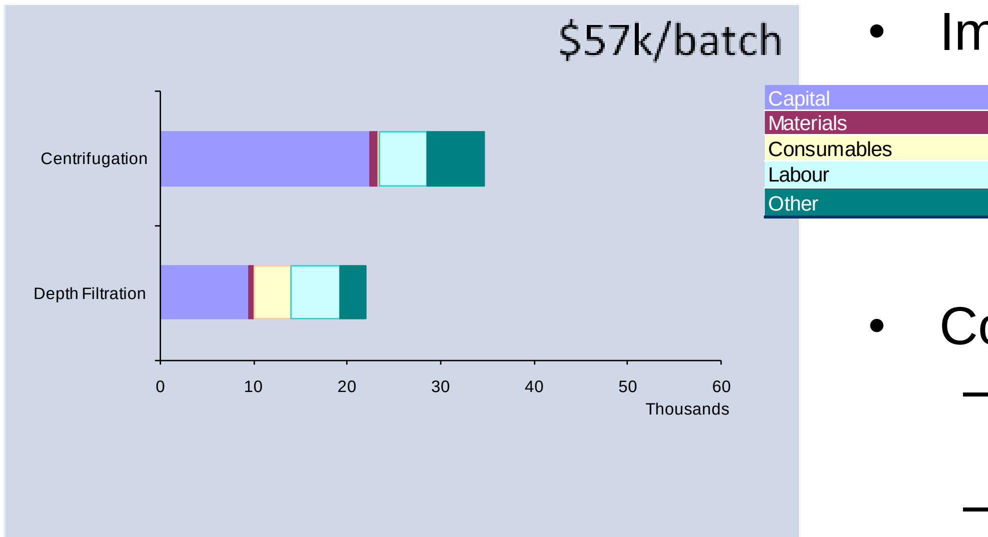
Location: New build

- What if you choose an alternate location?

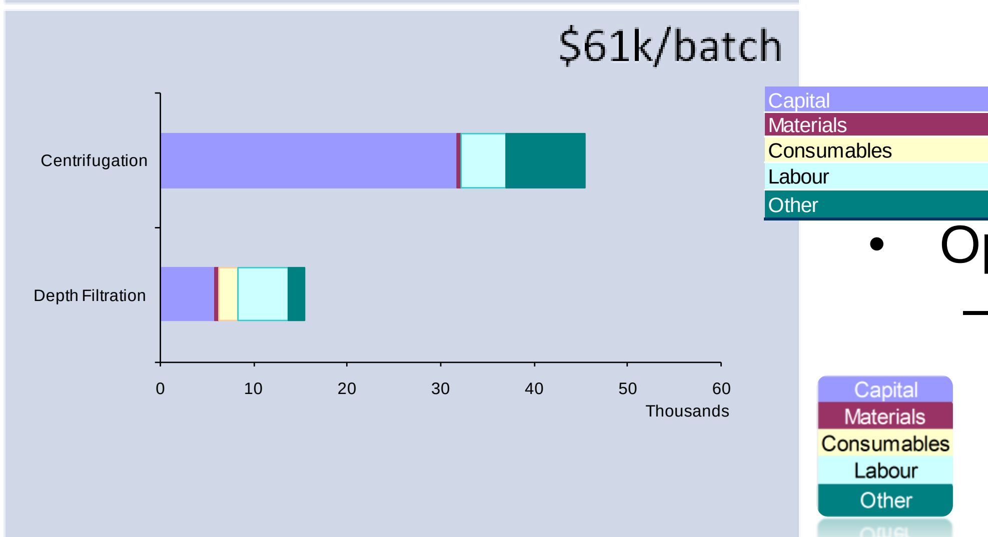
- Relevant issues
- Quick to implement in BioSolve
- Emphasis on understanding outcomes

Discussion Points

Non-Hermetic



Hermetic

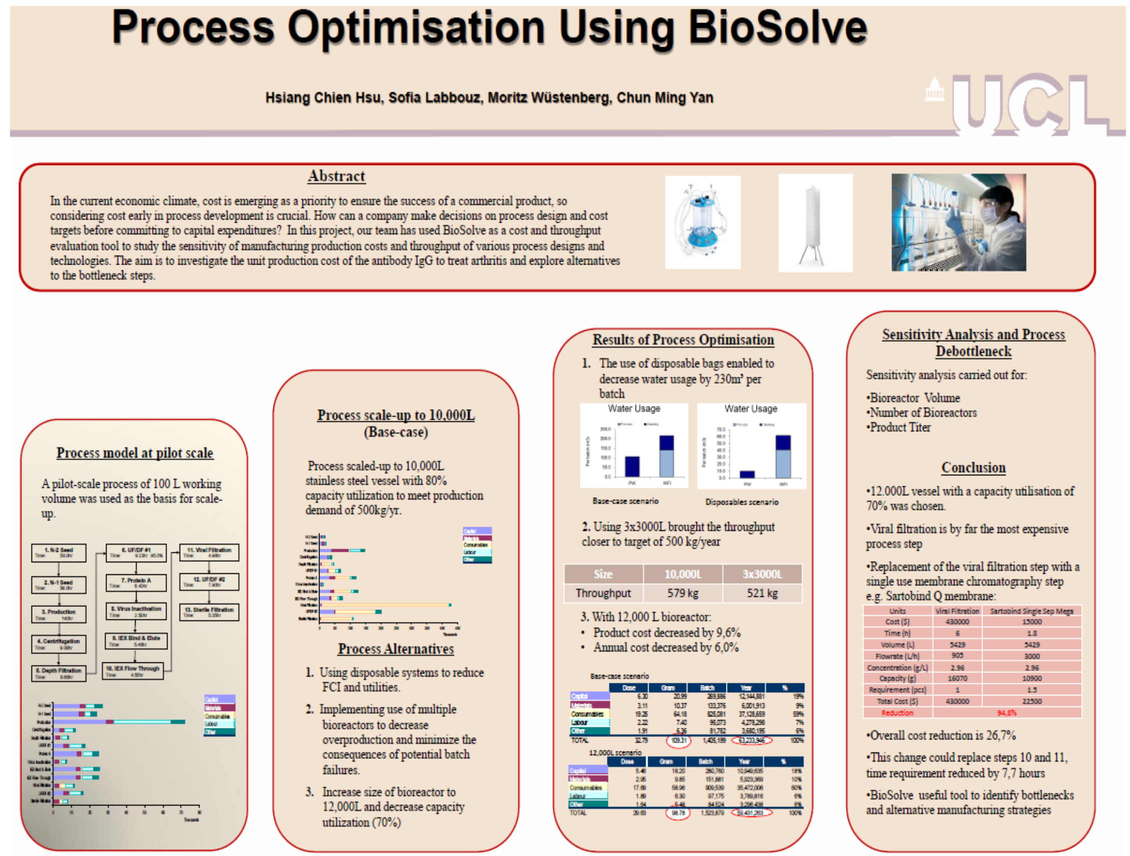


- Impact of design & operation
  - Depth filtration area required?
  - Overall economics of harvest operations?
- Cost breakdown
  - Largest contributing factor to predicted costs?
  - Proportion of equipment costs relating to support equipment?
  - What could be done to reduce costs?
- Operational constraints
  - 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.”



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:

UCL	Mike Hoare Yuhong Zhou Tarit Mukhopadhyay Daniel Bracewell Our UG and MSc students!
BioPharm Services Ltd:	Andrew Sinclair James Myers James Savery (now MedImmune)