

Process Economic Modeling for Decision-Making during Process Development of Therapeutic Proteins

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Production and Economics of Biopharmaceuticals

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Historical Background

- Recombinant protein discovered as part of the in-house functional genomics program
- *E. coli* derived protein chosen for accelerated development and proof-of-concept Phase I studies were completed
- Projected high COGs necessitated looking into alternative production methods and a CHO-derived process was developed
- The direct costs for the production of CHO-derived protein were 75% lower than the direct costs for the production of E. coli-derived protein
- Direct costs of production of CHO-derived protein, using currently existing facilities, constituted <10% of the COGM

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COGM Parameters

Direct Costs

- Raw Materials
- Operating Labor

Fixed Charges

- Depreciation of Capital
- Taxes and Insurance

Plant Overhead

- Supervisory Labor
- Maintenance
- QA/QC costs
- Supplies

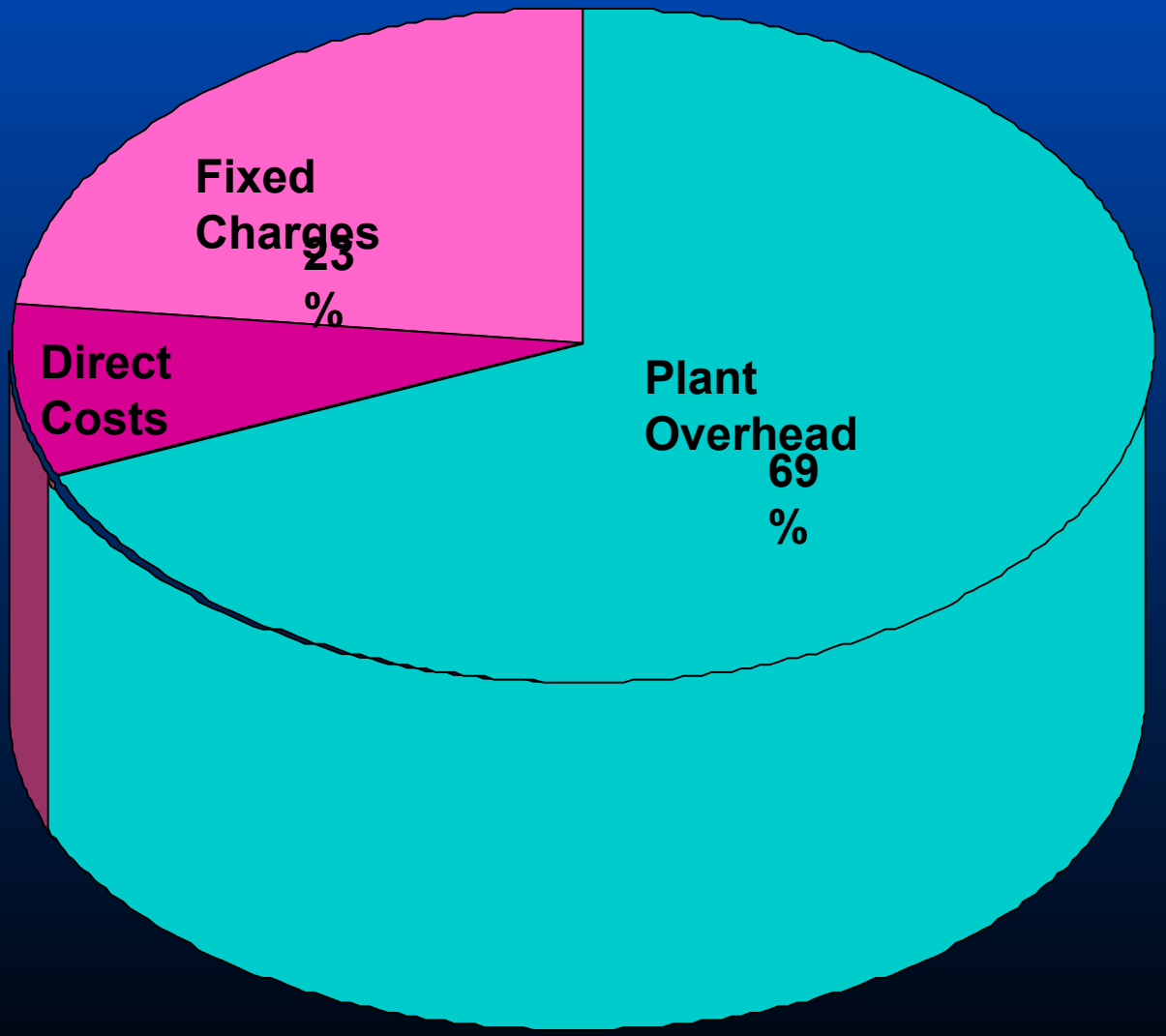
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Direct Cost Parameters

- **Raw Materials**
- **Operating Labor**
- ***Power and Utilities***
- ***Waste Disposal***
- ***Royalties***

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COGM Breakdown



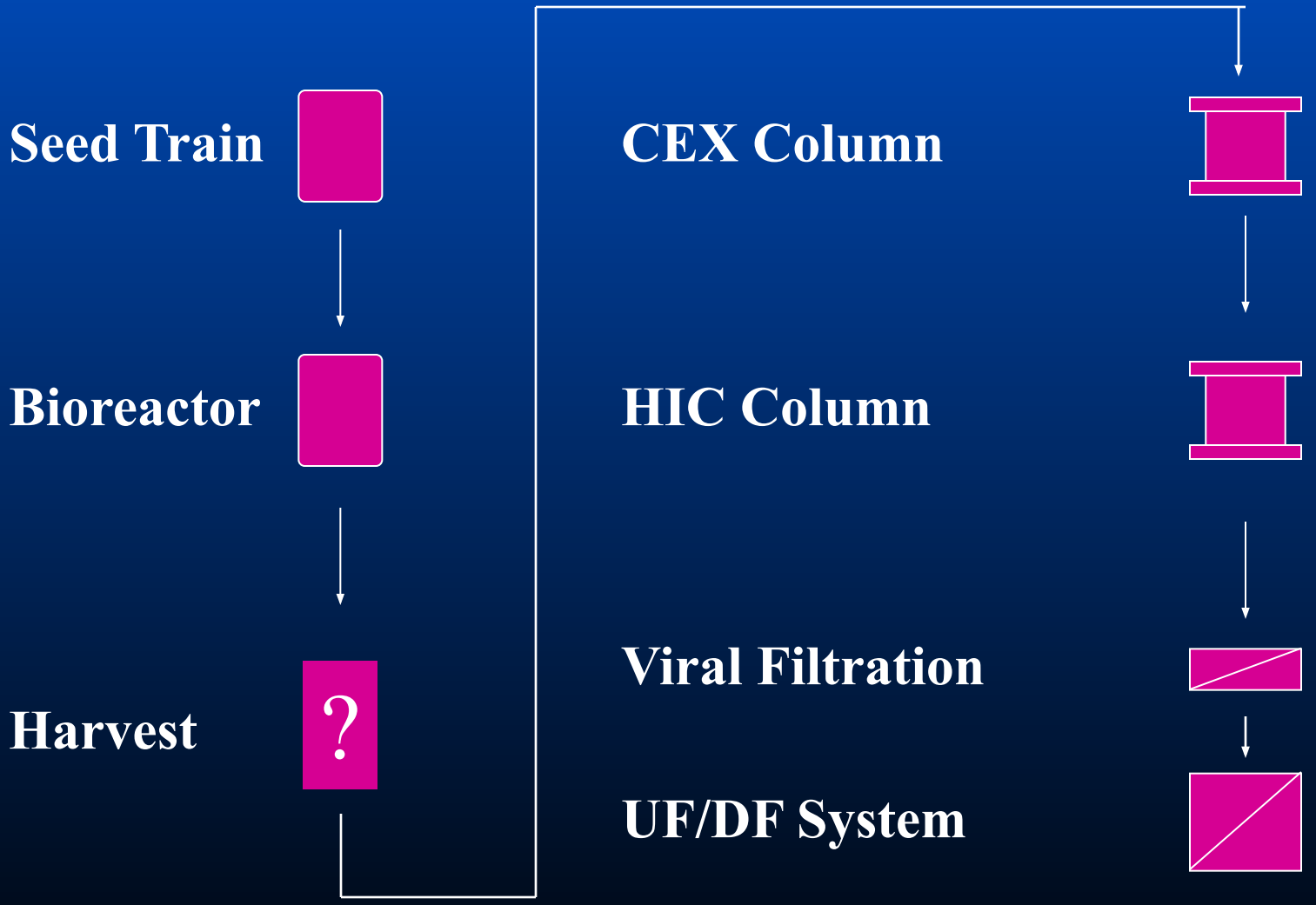
Objective of this work

Assuming that we were going to build a new, dedicated facility and be allowed to optimize scheduling, we would want to:

- Understand what drives large scale production economy
- Understand how Process Development can influence the economics

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Process Flow Diagram



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Process Summary

- 4 Downstream Steps
- Step Yields 87-100%
- Two high resolution steps
- One built-in hold step

- OVERALL YIELD: 52%

- TARGET PRODUCTION: 500kg/y

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Net Present Value (NPV)

- Money received or paid over time is not worth as much as money today
- Investing money implies a lost opportunity cost.
- Net Present Value is a way of discounting cash flows which occur in the future to their present value
- "Cost of Capital" is the required discount rate
- It is always better to:
  - Have positive cash flows early
  - Have negative cash flows later

$$PV = \frac{FV}{(1+i)^n}$$

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Cash Flows Which Go Into NPV

- Revenue $
- Manufacturing Costs
- General Expenses
- Capital Expenitures
- R&D
- Clinical Development
- ...

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Dealing With Uncertainty

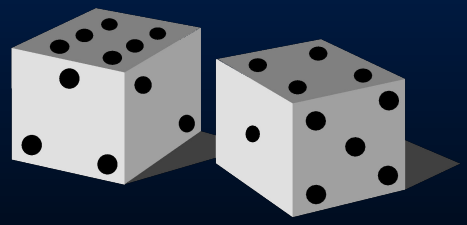
It is difficult to accurately predict the magnitude of future cash flows. Multiple sources of uncertainty exist

- Process Yields
- Lot Failures
- Forecasted materials and equipment prices
- Sales projections
- Natural disasters
- etc….

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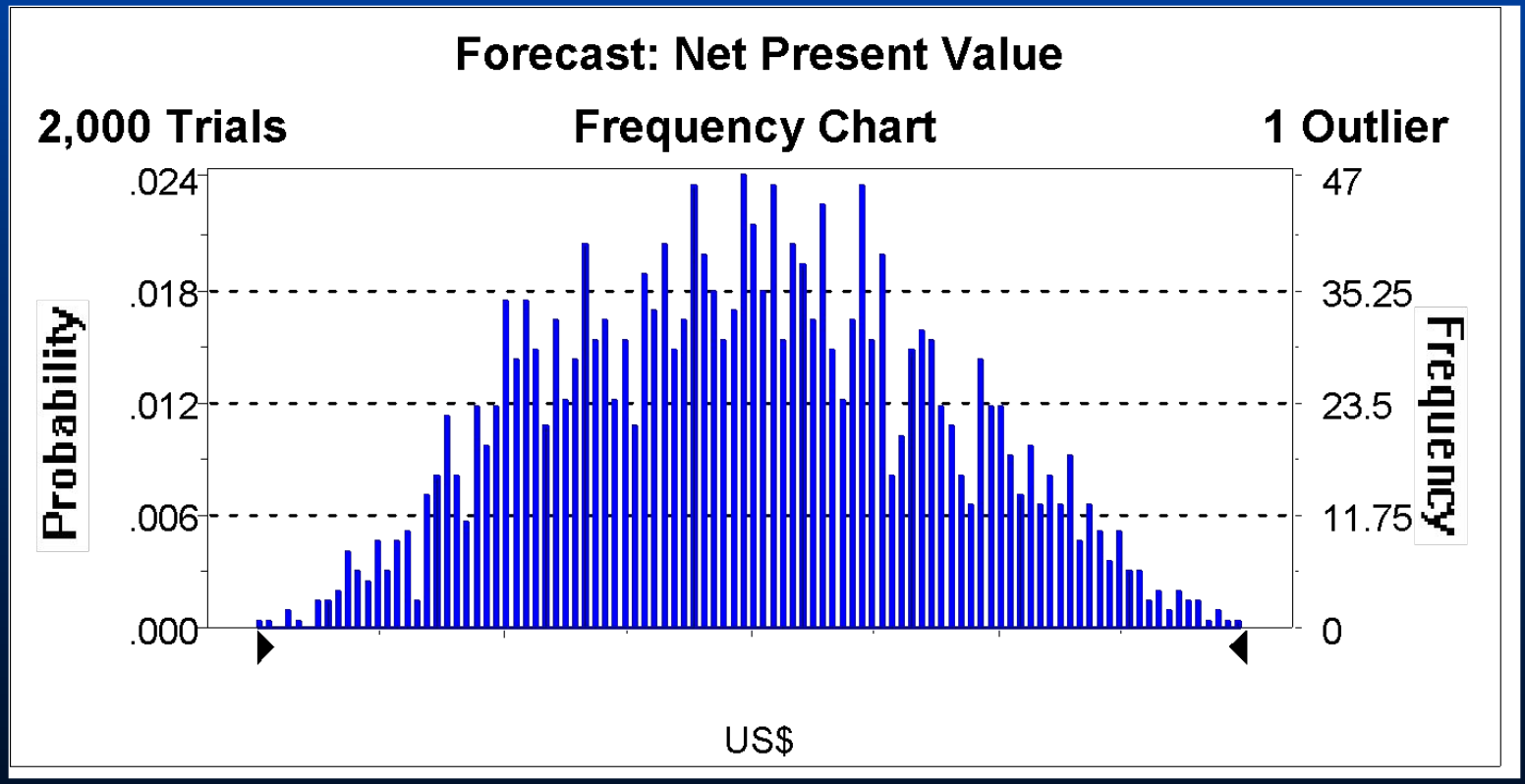
Dealing With Uncertainty

- Monte Carlo Analysis
  - Define Ranges for each of your unknowns
  - Roll the dice and see what happens
  - Excel add in tools make this easy



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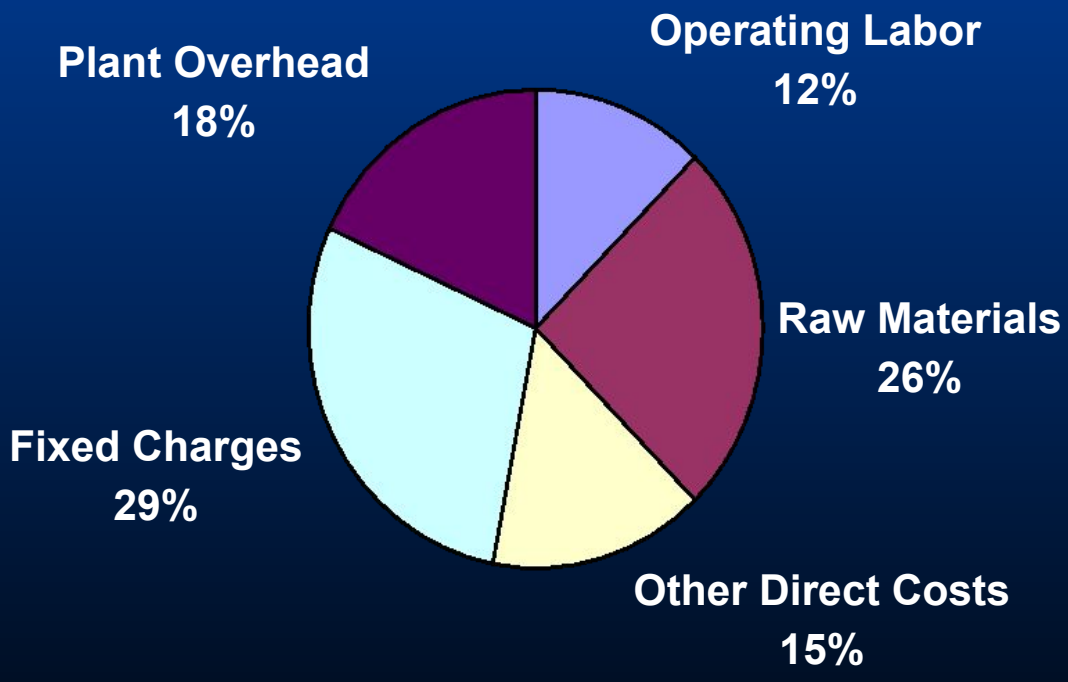
NPV of Base Case
TFF Harvest, 1 week Bucket



>99.999% confidence that NPV is positive

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Manufacturing Cost Breakdown



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Cycle Times by Unit Operation

Operation	Cycle Time (h)
Production Culture	240
TFF Microfiltration	8
Affinity Chromatography	3 x 3 = 9
Cation Exchange Chromatography	4.6
Hydrophobic Interaction Chomatography	8.2
Ultrafiltration	8

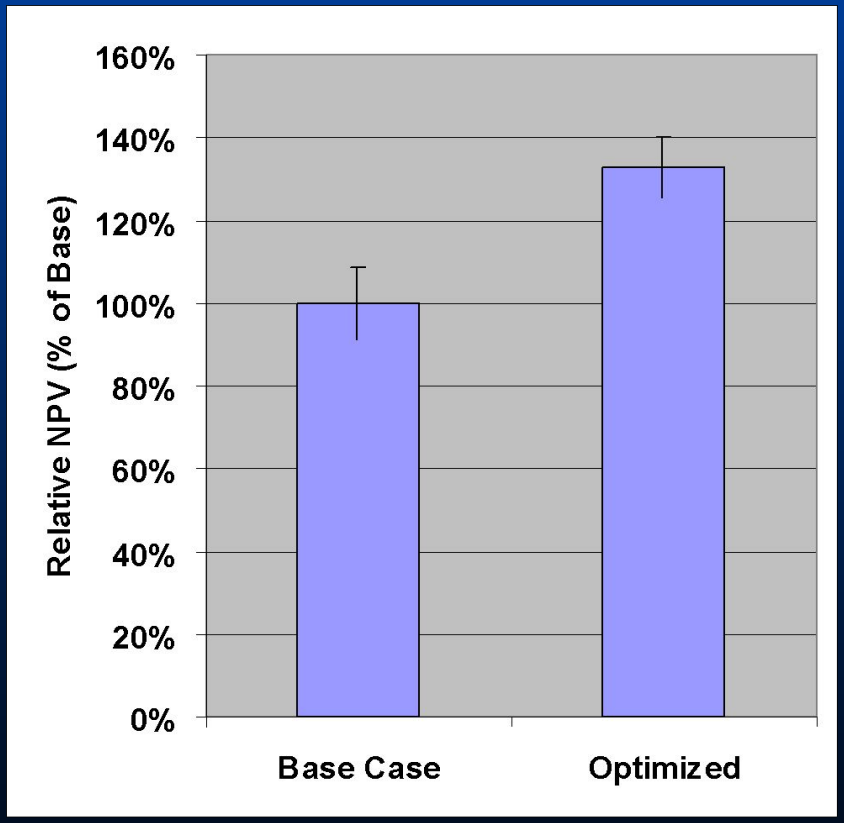
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Economic Impact of Concurrent Processing

- Much smaller capital equipment
- Much smaller chromatography columns
- Many more reuses of resins

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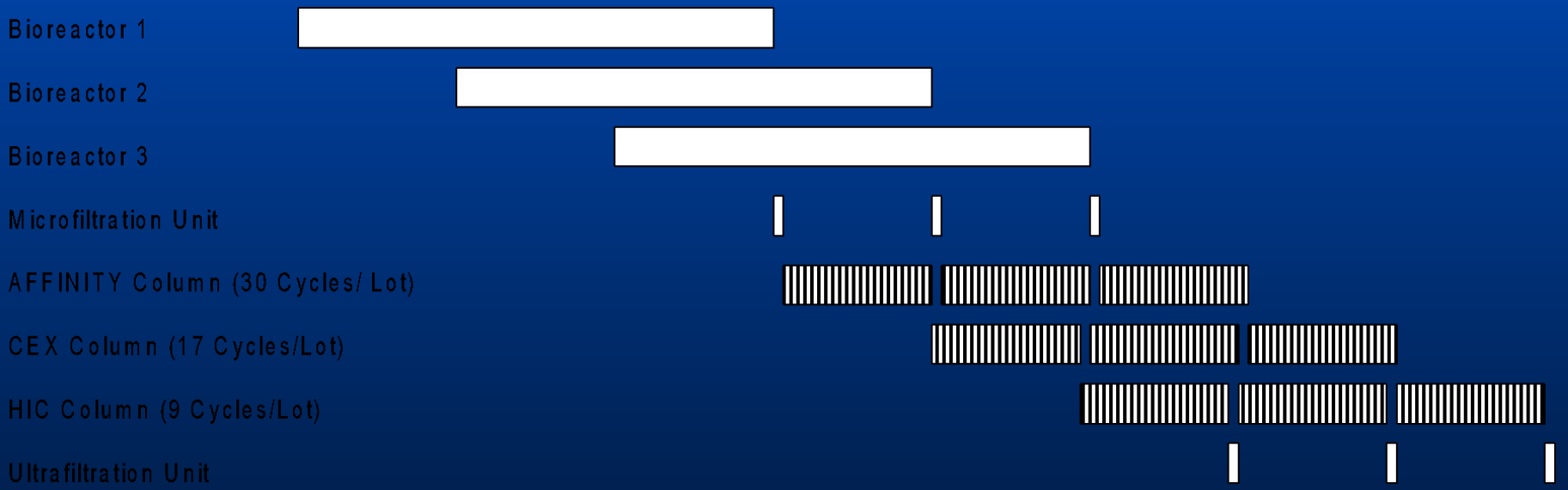
Comparison of NPV for Optimal Scheduling



- Optimized NPV 132% ± 7% of the base
- >99.999% certainty that this is better than base case
- Process must be designed with this in mind

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Equipment Utilization



Affinity Column	147L ---> 15L
CEX Column	833L ---> 49L
HIC Column	917L ---> 102L

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Implications of Concurrent Processing

- There must be a built in hold step
- Cycle times on all operations must be equal
- No Reprocessing
- High level of automation
- Demonstration of reuse of materials is economic necessity

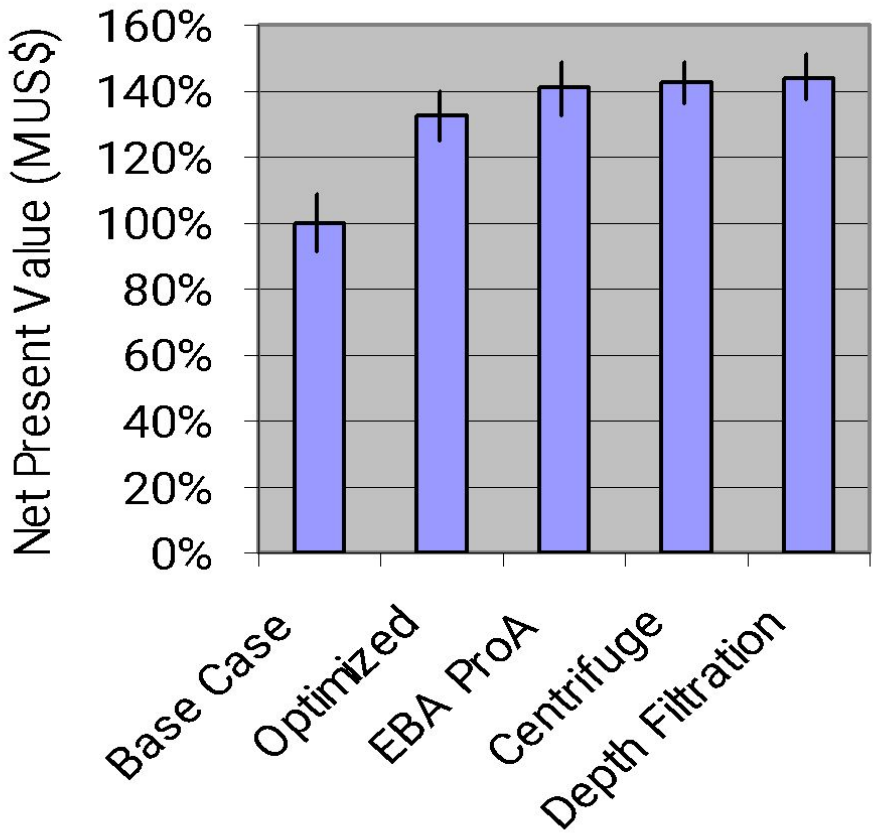
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Harvest Alternatives

- TFF (base case)
- Expanded Bed
- Centrifugation
- DE filtration

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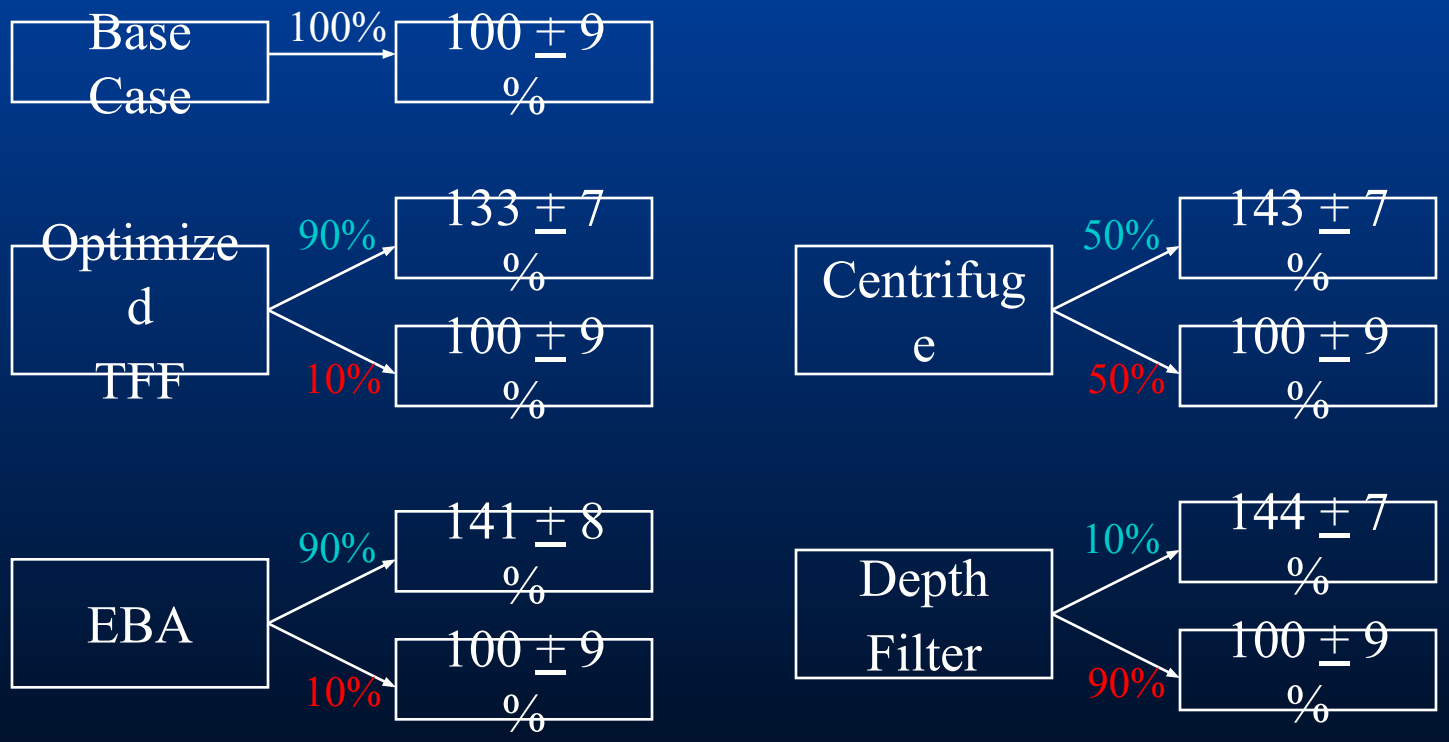
Comparison of Alternatives



- NPV's for all Optimized Alternatives look similar
- What about the risks??

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Decision Tree for Comparison of Alternatives



Risk Adjusted Comarison

Alternative	Median Savings (% Base NPV)	Maximum Development $ (% Base NPV)
Cycle Optimization	30%	12%
EBA Affinity	37%	14%
Centrifugation	21%	(15%)
Depth Filtration	1%	(22%)

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Concluding Remarks

- Process Development Decisions Greatly impact Process Economics
- Process Development influence is not limited to yield improvement and materials cost reduction

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- Glenn Hunter
- Oliver Kaltenbrunner

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