BIOPROCESS SIMULATION, ECONOMICS AND DESIGN

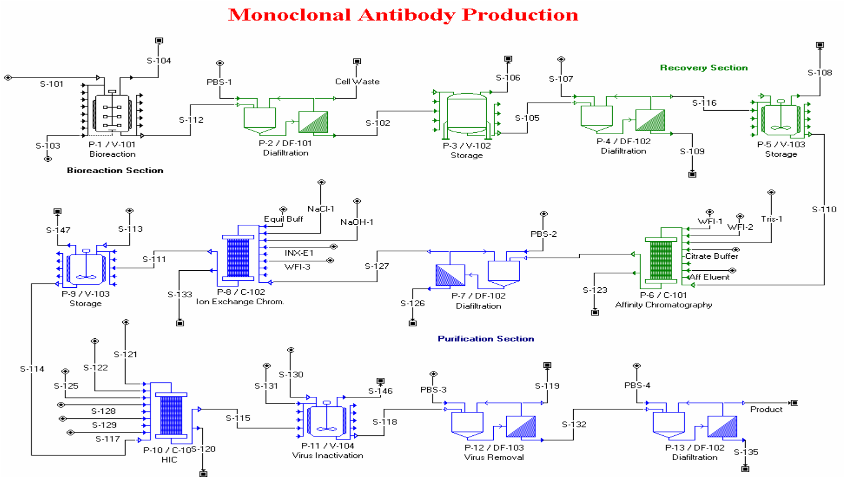
CHARLES L. COONEY

DOWNSTREAM PROCESSING COURSE

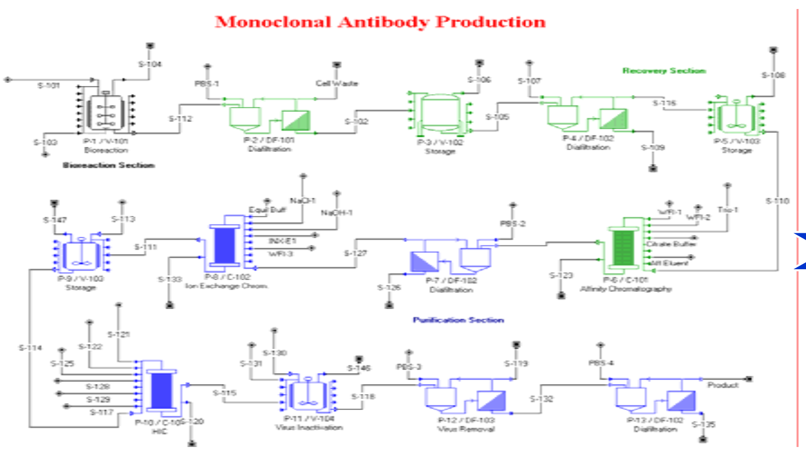
MIT, CAMBRIDGE, MA

PROCESS SYNTHESIS & PROCESS ANALYSIS

Where do you begin Process Design?



Information on Products, raw materials, etc.



M&E balances, sizing, costing, economic evaluation

YOUR GOAL

IF YOU DON'T KNOW WHERE YOU ARE GOING AND YOU DON'T HAVE A MEANS OF MEASURING WHERE YOU ARE THEN YOU WON'T KNOW WHEN YOU ARRIVE

STEPS IN PROCESS DESIGN

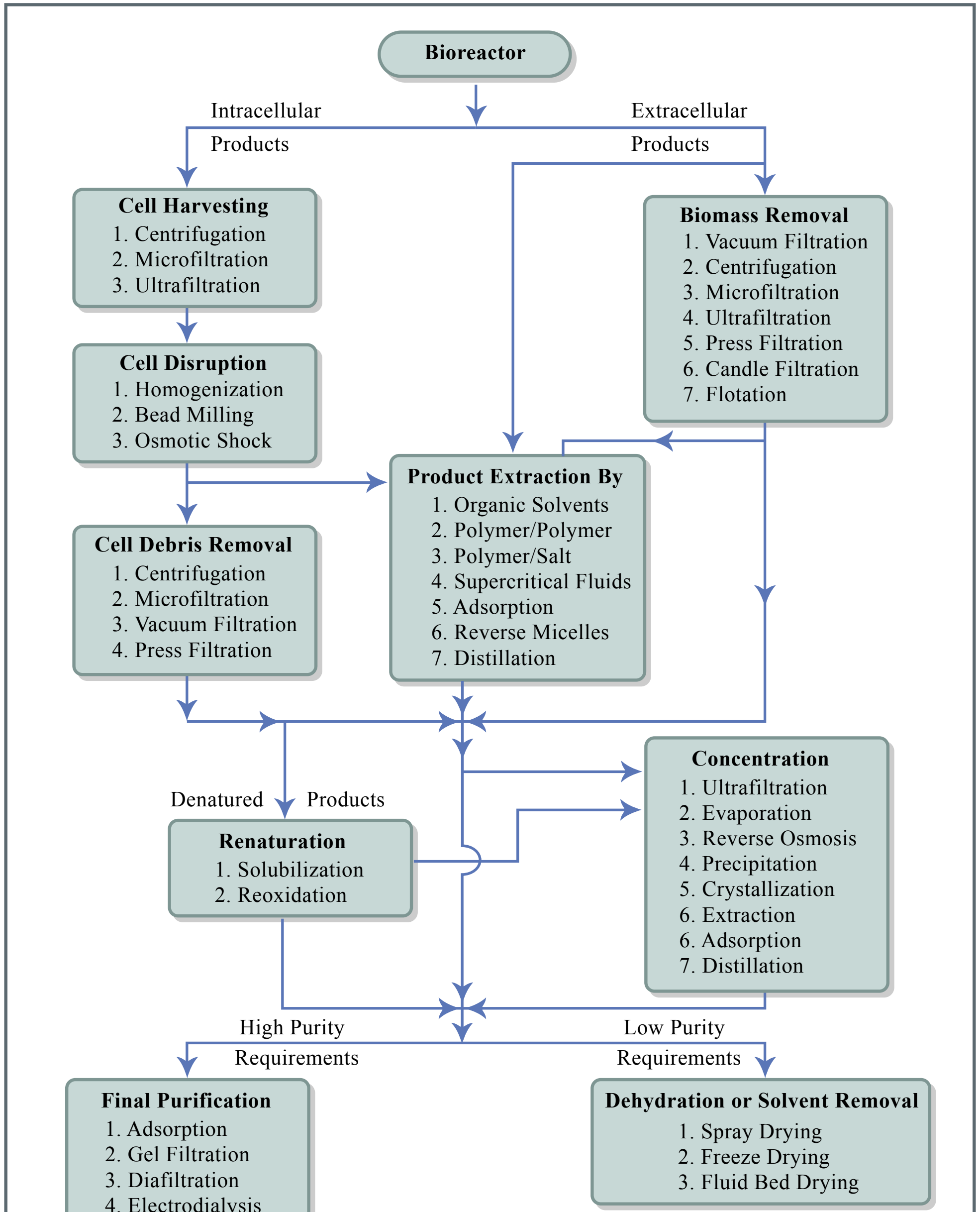
1. Product definition
   - Product specifications
   - Defines analytical needs
   - Market size
2. Select the synthetic technology
3. Create process flow diagram (PFD)
4. Material & energy balances to calculate costs
   - Materials (reagents and consumables)
   - Equipment
   - Utilities
   - Labor
5. Assess assumptions and uncertainty
6. Identify economic and quality hot spots
7. Assess profitability and risk
8. Create the R/D agenda

WHAT DO I WANT & NEED TO KNOW FOR PROCESS MODELING AND SIMULATION

- What is the cost of goods?
- What are the cost sensitive operating parameters?
- What are the assumptions and where is the uncertainty?
- Where are the economic hot spots?
- Where should one focus R&D?
- What is the impact of process change on cost and quality?
- Are there alternative processes?
- Where are the process bottlenecks?
- How can I increase throughput & profitability?

$$PROFIT = VF_M (S_P S_A - C_M)$$

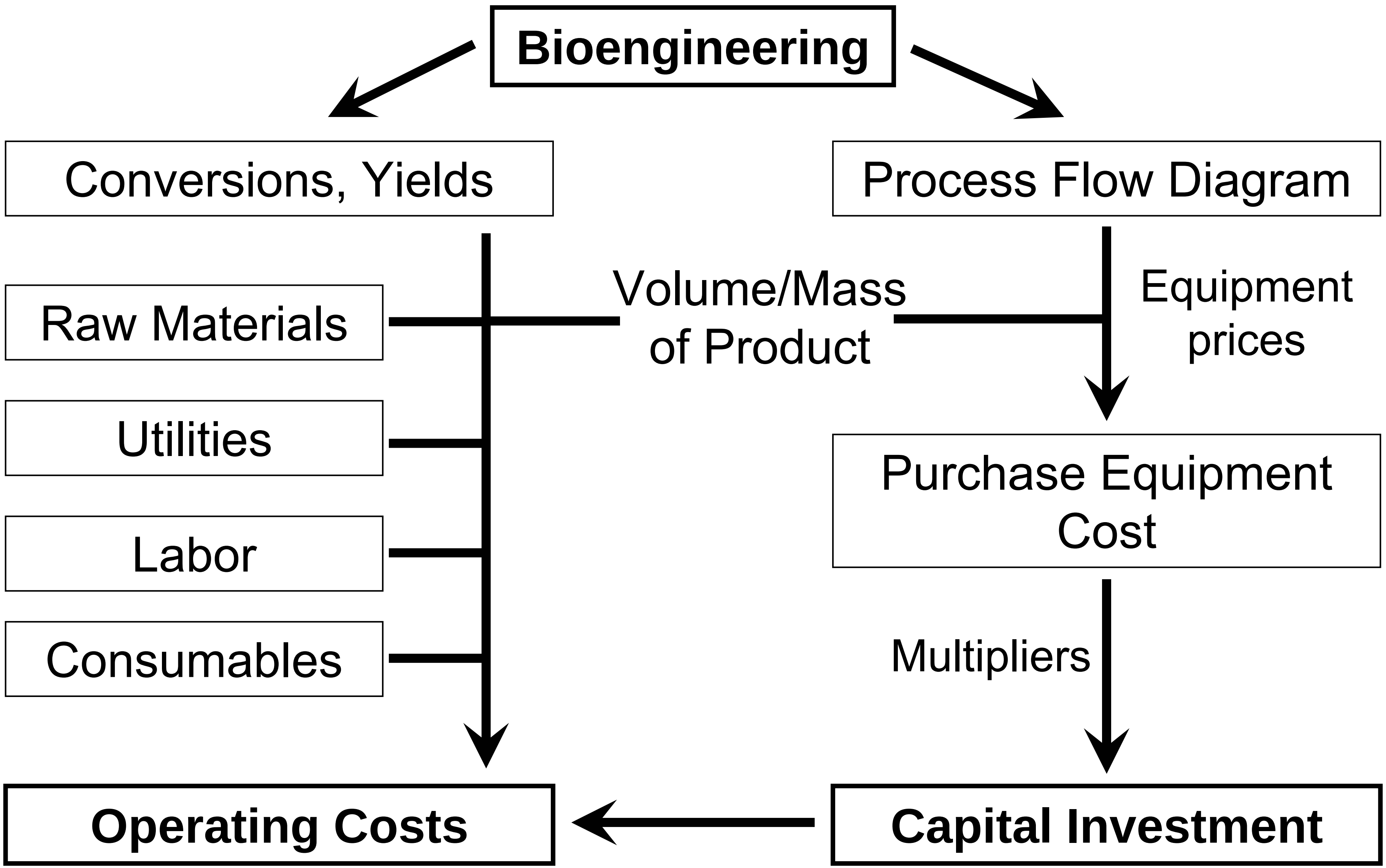
WHEN SELECTING UNIT OPERATIONS THERE ARE CHOICES AND DECISIONS MUST BE MADE



Contemporary Downstream Processing of Biological Materials

Figure by MIT OCW.

Overview



Bioengineering
Conversions, Yields
Process Flow Diagram
Raw Materials
Volume/Mass of Product
Equipment prices
Utilities
Purchase Equipment Cost
Labor
Multipliers
Consumables
Operating Costs
Capital Investment

CASE STUDIES

- **Protein synthesis using mammalian cells for Monoclonal Antibody production**

- **Microbial process producing the antibiotic Penicillin**

- **Alkaline Protease production by microbial fermentation**

CASE OBJECTIVES

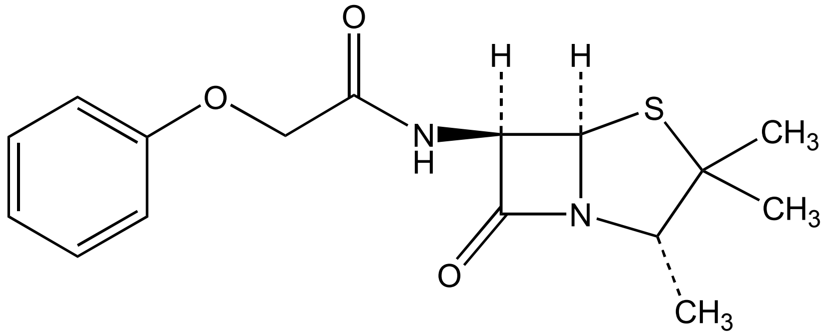
- Flowsheet formulation
- Material and energy balances
- Equipment size estimation
- Estimation of capital costs
- Estimation of operating cost
- Profitability
- Assay for the process

Monoclonal Antibodies

- *In vitro* use (antigen identification, antigen purification)
- *In vivo* use (therapeutic applications, diagnostic tools)
- Growing market: 2,400 kg in 2006 (Chovav et al., 2003)
- New MAb entering the market; in the biopharmaceutical development pipeline
- Need for new production facilities and optimization of existing plants

Chovav et al.: The state of biomanufacturing; UBS's Q-series: London, 2003.

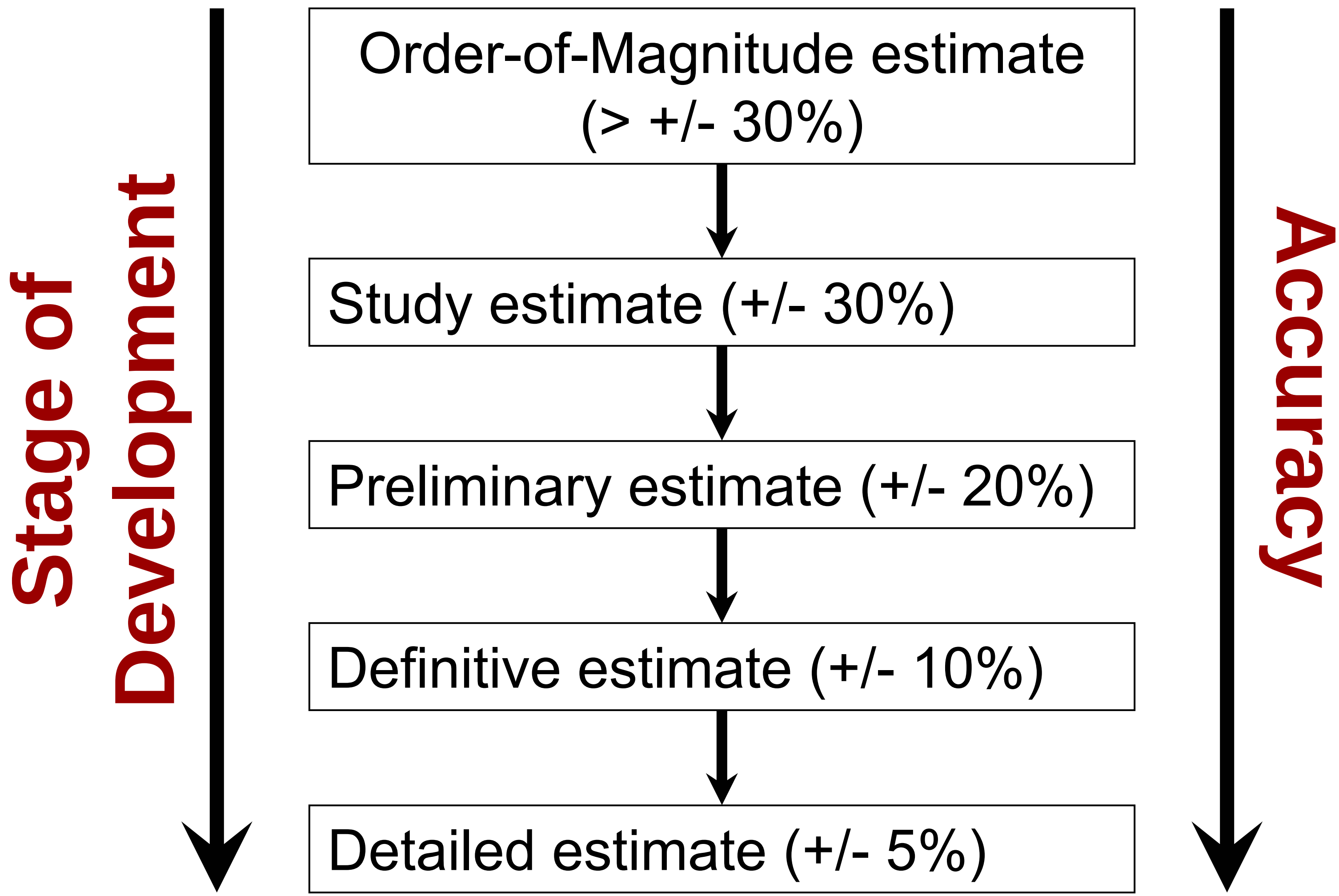
Penicillin V



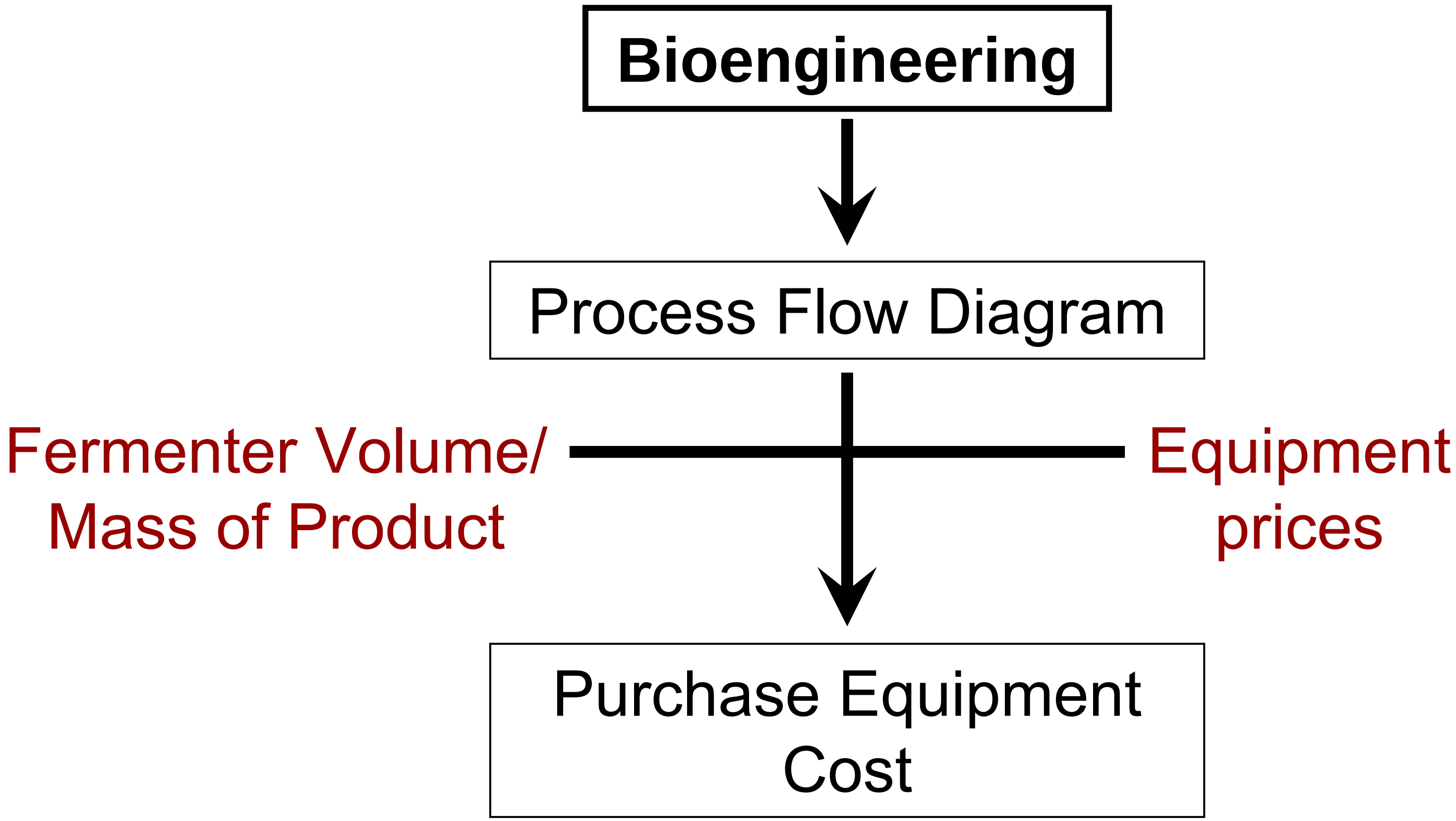
- Hydrophobic β-lactam
- Produced by *Penicillium chrysogenum*
- Penicillin G and V main penicillins of commerce
- Used a human medicine and in animal health
- Further processed to semi-synthetic penicillins
- Annual production penicillin: 65,000 tons
- Price penicillin V: $11/BU, or $17-18/kg

1. Estimation of Capital Investment

Types of Cost Estimates



Equipment Size and Cost



Fermenter Size/ Amount of Product

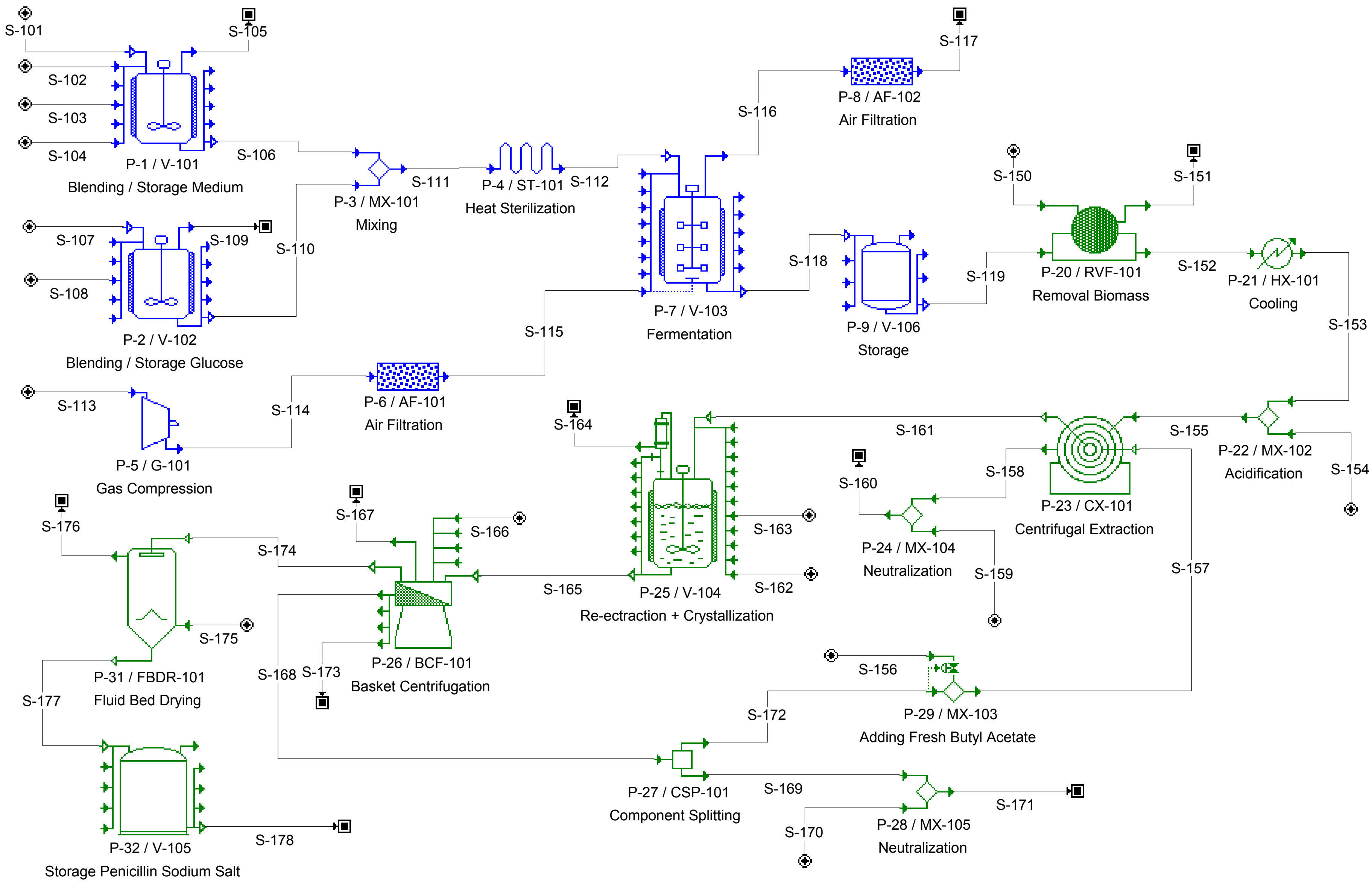
Plant size can be derived from:

- Volume and number of fermenters
- Annual amount of product to produce

Decision based on:

- Market Volume
- Technical feasibility
- Own business plan / competitor

Process Flow Diagram: Penicillin



Equipment Cost

- Costs for major pieces of equipment in PFD
- Prices obtained from:
  - Vendor quotations
  - Previous projects
  - Literature (e.g. Peters et al.)
  - Default values simulation software
- Cost estimate for unlisted equipment

Peters, M., Timmerhaus, K. and West, R.: Plant design and economics for chemical engineers; McGraw Hill: Boston, 2003.

Price Indices

- Purpose: To estimate cost data from previous projects, analogous sources, different times, etc.
- Most frequently used *Prices Indices*:
  - Marshall & Swift Index (M&S Index)
  - Chemical Engineering Index
- Estimating the cost:

$$\text{Present cost} = \frac{\text{(original cost) x (Index value Today)}}{\text{(Index value at time original cost was obtained)}}$$

Total Plant Direct Cost

Purchased Equipment Cost (PC)				**$ 12.4 Million**
Installation	1.0	X(PC)	=	12.4
Process Piping	0.75		=	9.3
Instrumentation	0.8		=	9.9
Insulation	0.05		=	0.6
Electrical	0.15		=	1.9
Buildings	2.5		=	31.0
Yard Improvement	0.15		=	9.9
Auxiliary Facilities	0.8		=	10.7
Total Plant Direct Cost				**$ 89.3 Million**

Direct Fixed Capital Investment

Total Plant Direct Cost (TPDC)				**$ 89.3 Million**
Engineering	0.25	X(TPDC)	=	22.3
Construction	0.35		=	31.2
Total Plant Indirect Cost (TPIC)				**$ 53.6 Million**
Total Plant Cost = TPDC + TPIC				**$ 142.8 Million**
Contractor's Fee	0.06	X(TPC)	=	8.6
Contingency	0.1		=	14.3
Direct Fixed Capital				**$ 165.7 Million**

Total Capital Investment

Direct Fixed Capital (DFC)			**$ 165.7 Million**
Start up/Validation cost	0.05 DFC	=	8.3
Working Capital: 30 days*		=	0.7
Total Capital Investment (TCI)			**$ 174.7 Million**

* Covering labor, raw material, utilities and waste treatment cost

Economy of Scale

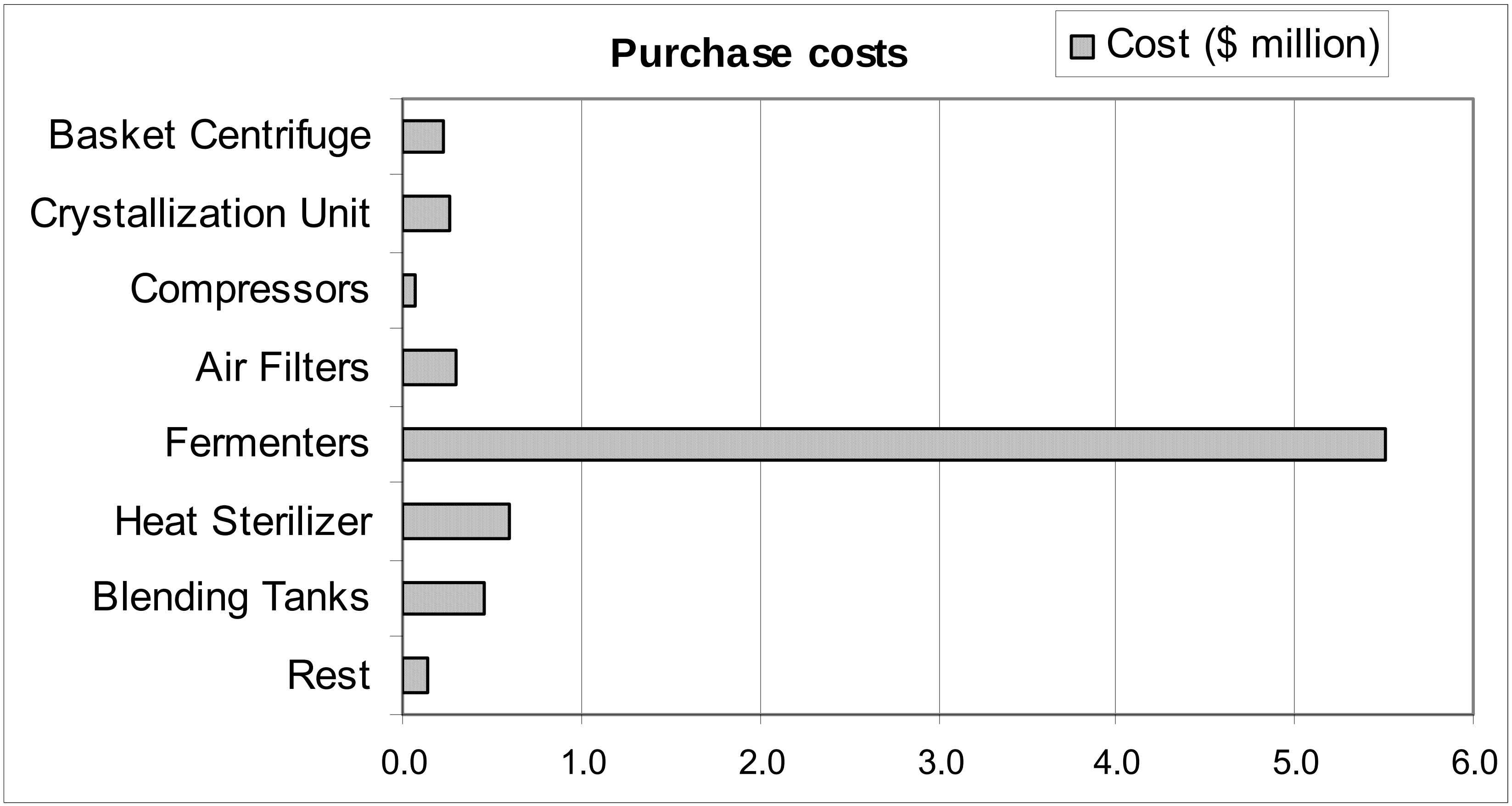
- Six-Tenth Factor:
  Derived from statistical/empirical data

$$K_2 = K_1\ (P_2/P_1)^{0.6}$$

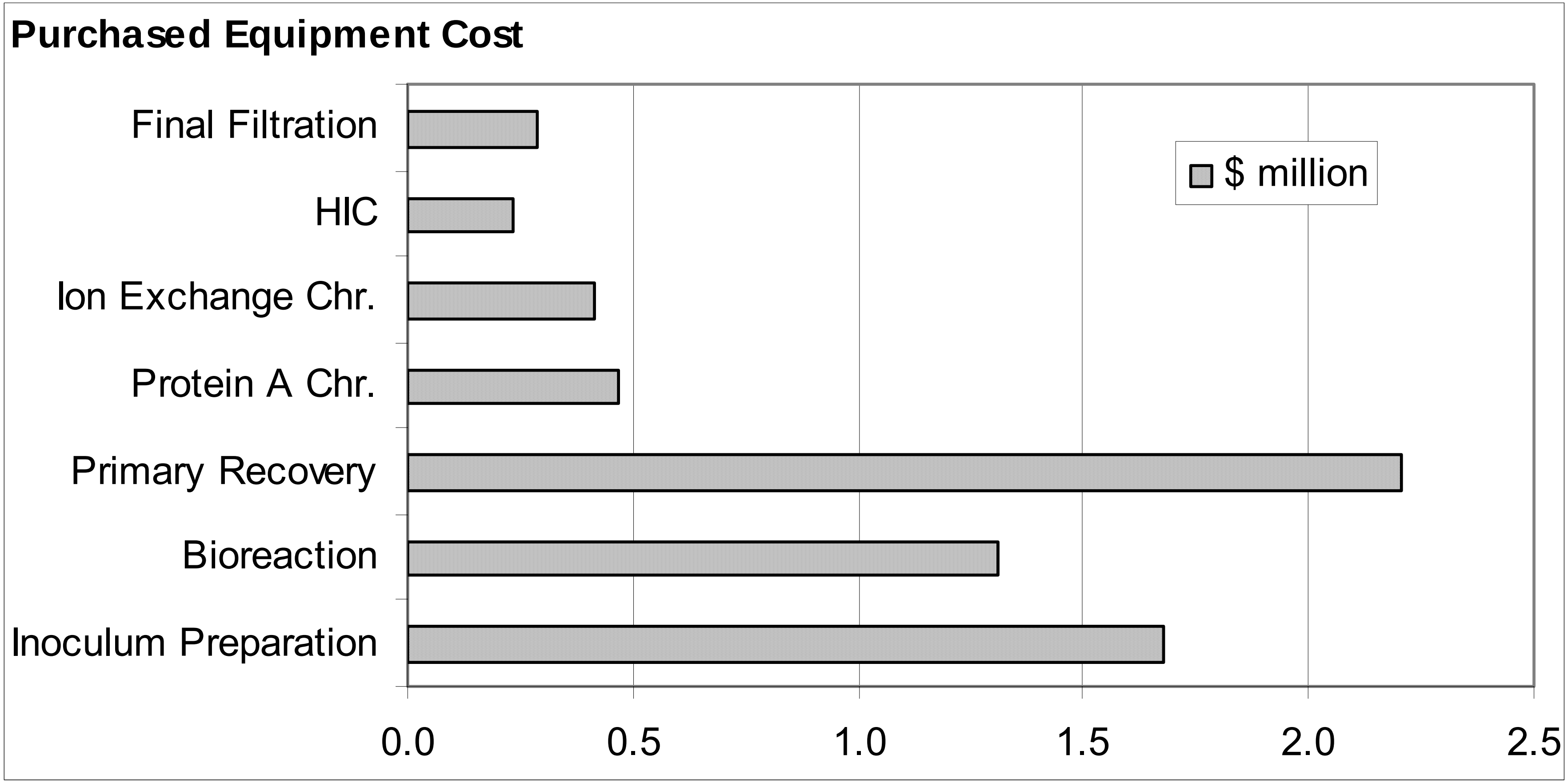
K = investment cost; P = annual capacity

- Example: MAb:
  - 381 kg MAb per year, \$175 Million investment cost
  - Estimated investment cost for a 500 kg plant:
    $K_2 = 175\ (500/381)^{0.6} = \$206$ Million

Penicillin:
Equipment Purchase Costs

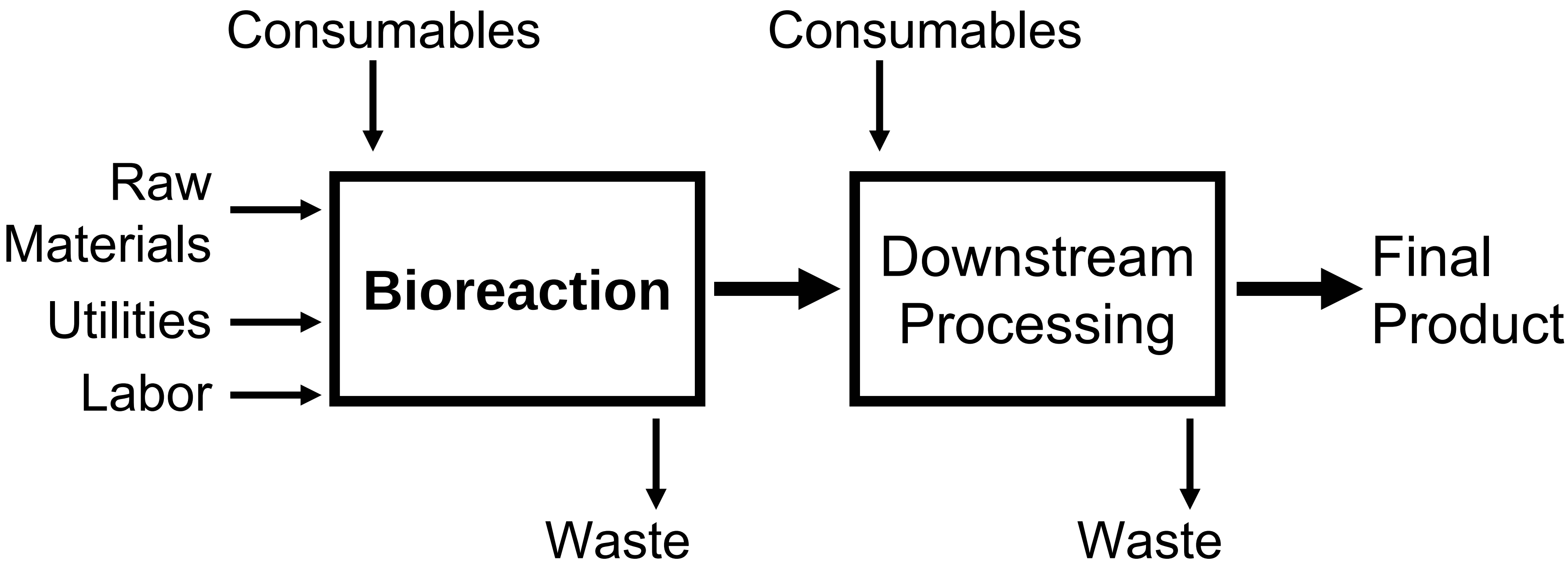


MAB: Allocation Equipment Cost to Sections



2. Estimation Operating Cost

Process Diagram



Raw Material Costs

- Amount of a compound x its Price
- Possible sources:
  - Supplier
  - Internal data
  - Literature, e.g. *Chemical Market Reporter*
  - Sales catalogues
- Pricing is very dependent on source and volume

Consumables

- Factors:
  - Amount per batch
  - Replacement frequency/ operating hours
  - Price
- Sources of data:
  - Experiments
  - Supplier data
  - Literature, default value simulation software
  - Estimates by analogy
- Major consumables:
  - adsorption/chromatography resins
  - membranes (filtrations, dialysis, diafiltration etc.)

Waste

- Waste treatment normally not part of the PFD
- Waste types and costs*
  - Solid waste:
    - Non-hazardous: $35/ton
    - Hazardous: $145/ton
  - Liquid waste/wastewater: $0.5/m^3
  - Emissions: cost depend on composition
- Treatment mandated by environmental laws

*Peters, M., Timmerhaus, K. and West, R.: Plant design and economics for chemical engineers; McGraw Hill: Boston, 2003.

Energy Consumption

- Typical energy consumptions:
  - Process heating & cooling
  - HVAC
  - Evaporation/distillation
  - Bioreactor aeration, agitation
  - Centrifugation, cell disruption, etc.
- Utility costs:
  - Electricity: 4.5 ct/kWh
  - Steam: 4.40 $/ton
  - Cooling water: 8 ct/m^3

Labor Cost

- Amount of labor:
  - Calculated from demand for each process step
  - Defines the number of people per shift/number of shifts
- Hourly cost
  - Internal company average value
  - Literature, e.g. Peters et al. (2003):
    skilled labor: 34 $/h
  - Bureau of Labor Statistics (www.bls.gov)

Depreciation

- Depreciation cost = “pay back” of investment cost
- Depreciation period ≈ Life time of project: 3-10 years
- Depreciation method:
  - Straight line (same $ every year)
  - Declining balance, e.g. MACRS

Facility-Dependent Costs: MAb

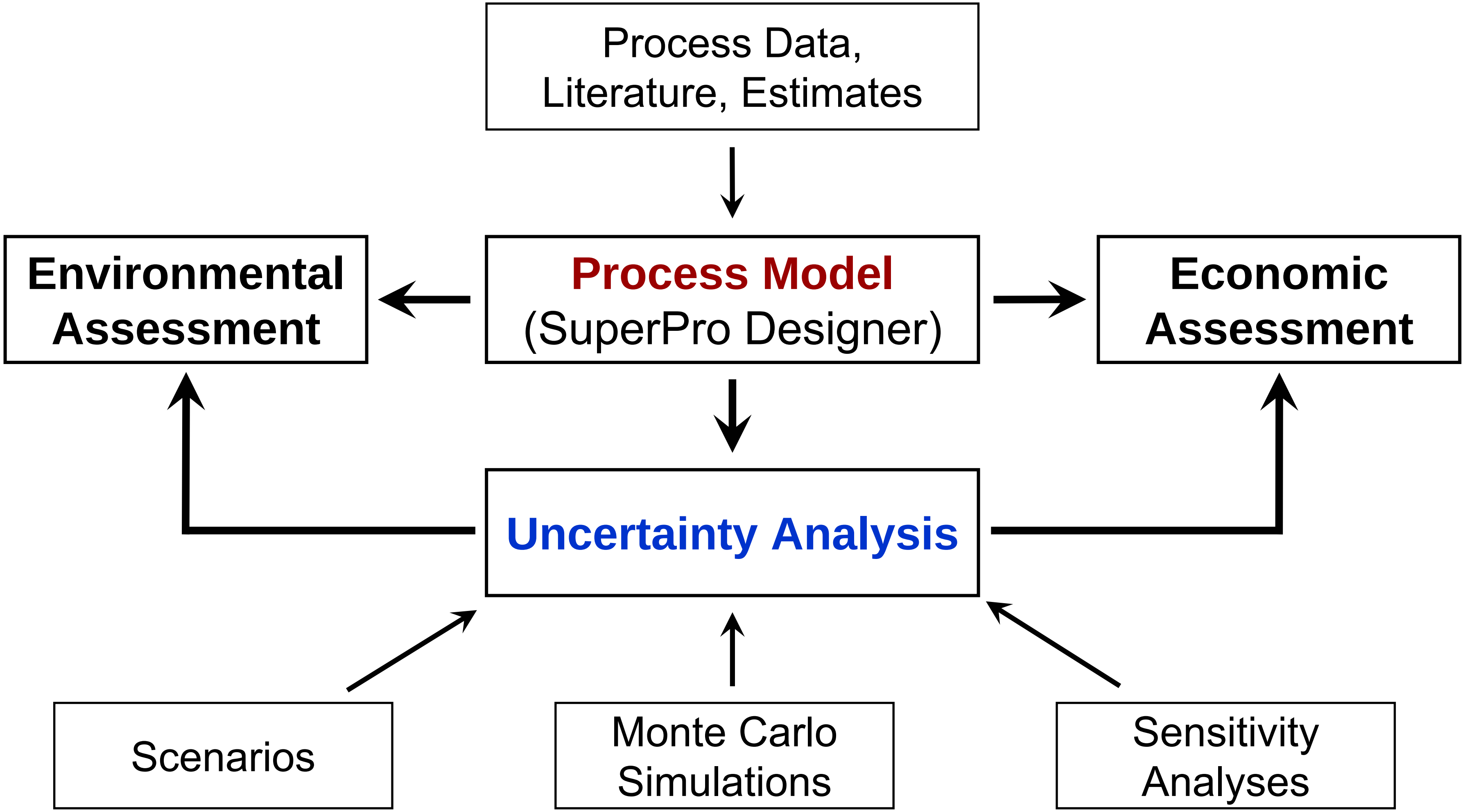
Direct Fixed Capital (DFC)				**$ 165.7 Million**
Insurance	0.015	DFC	=	2.5
Local Taxes	0.025	DFC	=	4.1
Contractor's Fee	0.055	DFC	=	9.1
Maintenance	0.06	DFC	=	9.9
Depreciation period	10 years			
Depreciation	0.10	TCI	=	16.6
Annual Facility-Dependent Cost				**$ 42.3 Million**

Operating Cost MAb

Raw Materials				3.5
Consumables				8.2
Total Labor Cost (TLC)				3.9
Utilities				0.024
Laboratory/QC/QA	0.6	TLC	=	2.3
Waste Treatment/Disposal				0.006
Facility-Dependent Costs				42.3
Operating Cost				**$ 60.3 Million**

3. Uncertainty Analysis

Uncertainty Analysis



Penicillin: Worst + Best Case Scenario

Objective Functions	Worst Case	Base Case	Best Case
Unit production Cost [$/kg]	28.0	16.0	10.5
EBITDA [$ million]	-18	4.0	31

Scenarios based on chosen minimum and maximum values for input variables

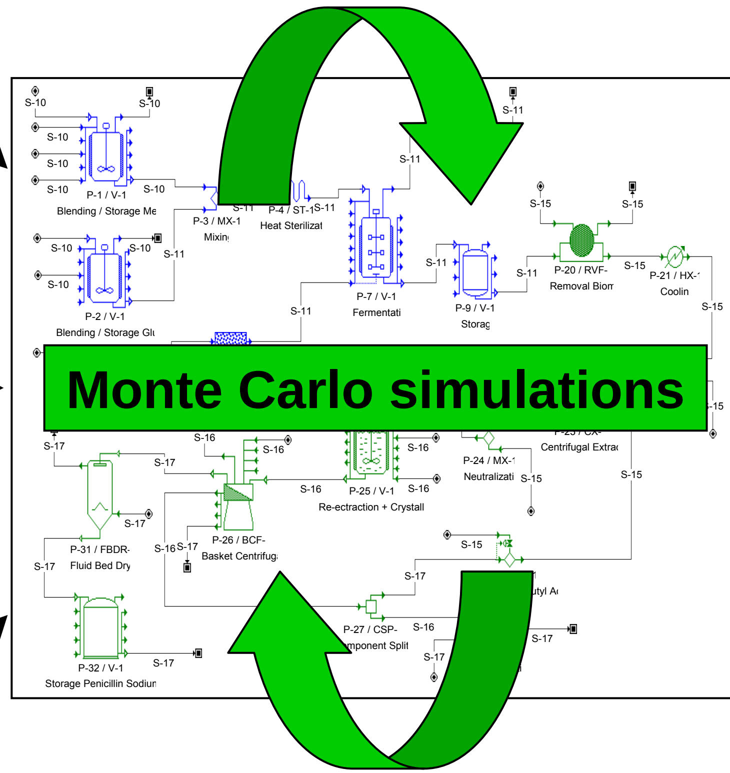
Monte Carlo Simulation

Uncertain variables:

Technical parameters
e.g. product concentration

Supply chain parameters
e.g. media price

Market parameters
e.g. product selling price



Objective functions:

Environmental Indices

Unit Production Cost

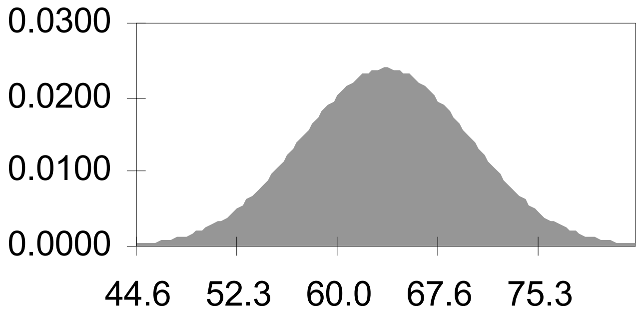
Return on Investment

Penicillin: Parameters for Monte Carlo Simulation

- Yield biomass on glucose
- Maintenance coefficient (glucose)
- Precursor utilization efficiency
- Final biomass concentration
- Final production concentration
- Aeration rate
- Agitator power

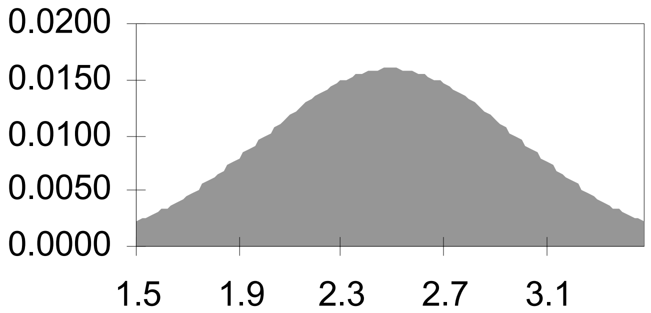
- Downstream recovery yields (each step)
- Recycling yields: butyl acetate, acetone
- Price glucose
- Price phenoxyacetic acid
- Electricity cost ($/kWh)
- Selling price product

Probability Distribution: Input Variables



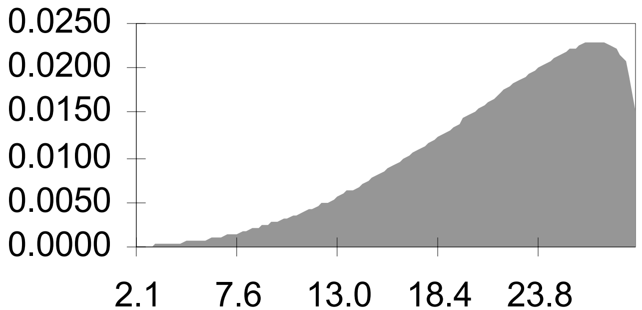
Final product concentration:

Normal distribution, Std.-Dev.: 10%



Agitator power:

Normal distribution, Std.-Dev.: 20%, min: 1.5 kW/m^3, max: 3.5 kW/m^3

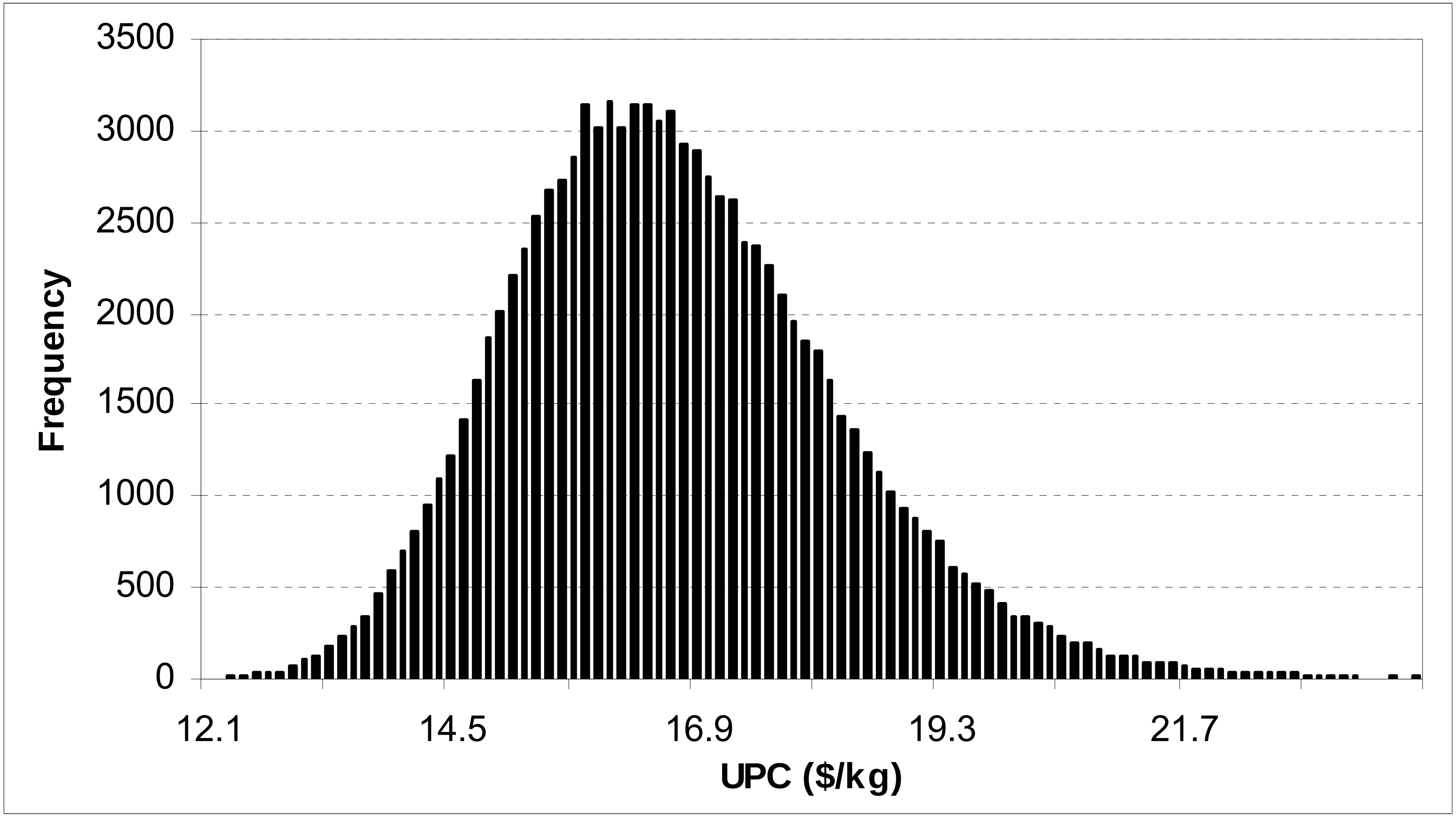


Price glucose:

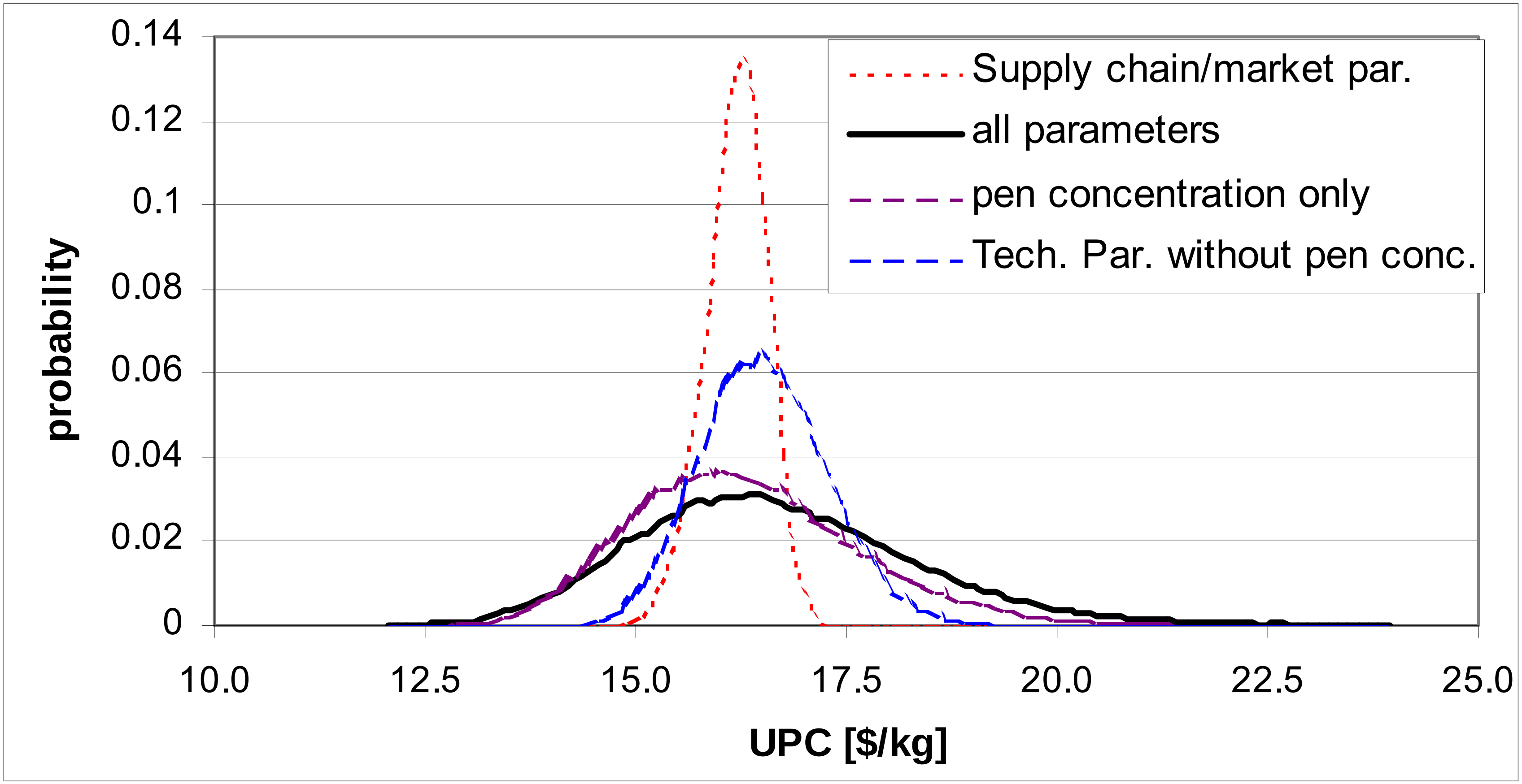
Beta distribution, α = 3.49; β = 1.2,

Distribution type fits best actual data

Probability Distribution UPC: Technical Parameters



Probability Distribution UPC Unit Cost



Production of Alkaline Protease for Detergent Use

Alkaline protease is an important additive for use in laundry detergents. The objective is to simulate the operation of a plant to produce 6,000 ton/y of crude enzyme (e.g. containing 250 tpa of pure protein). The plant will use five (5) 150 m^3 fermentors and operate with a 75 h process cycle time.

Production of Alkaline Protease

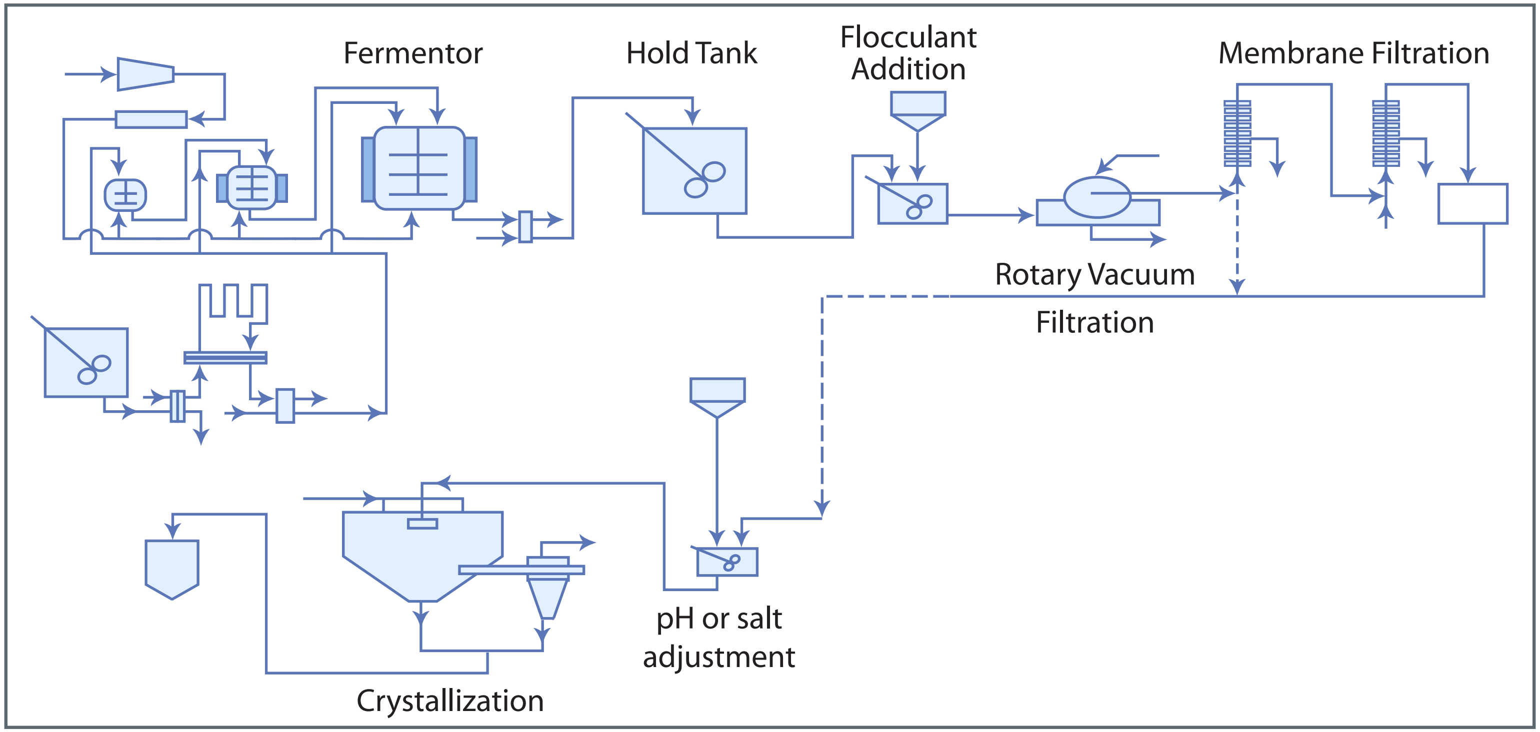


Figure by MIT OCW.

Alkaline Protease

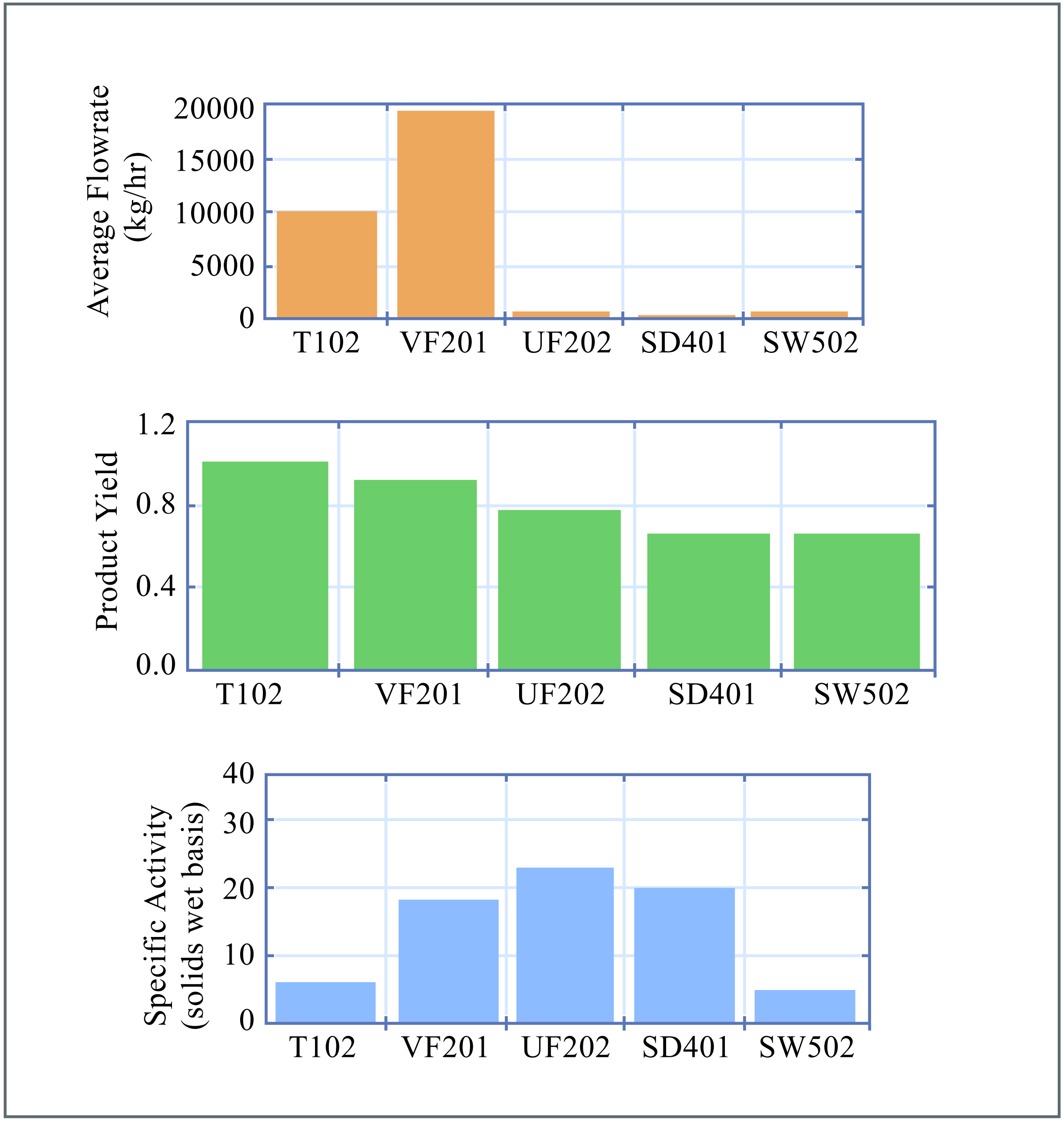


Figure by MIT OCW.

Improving Titer

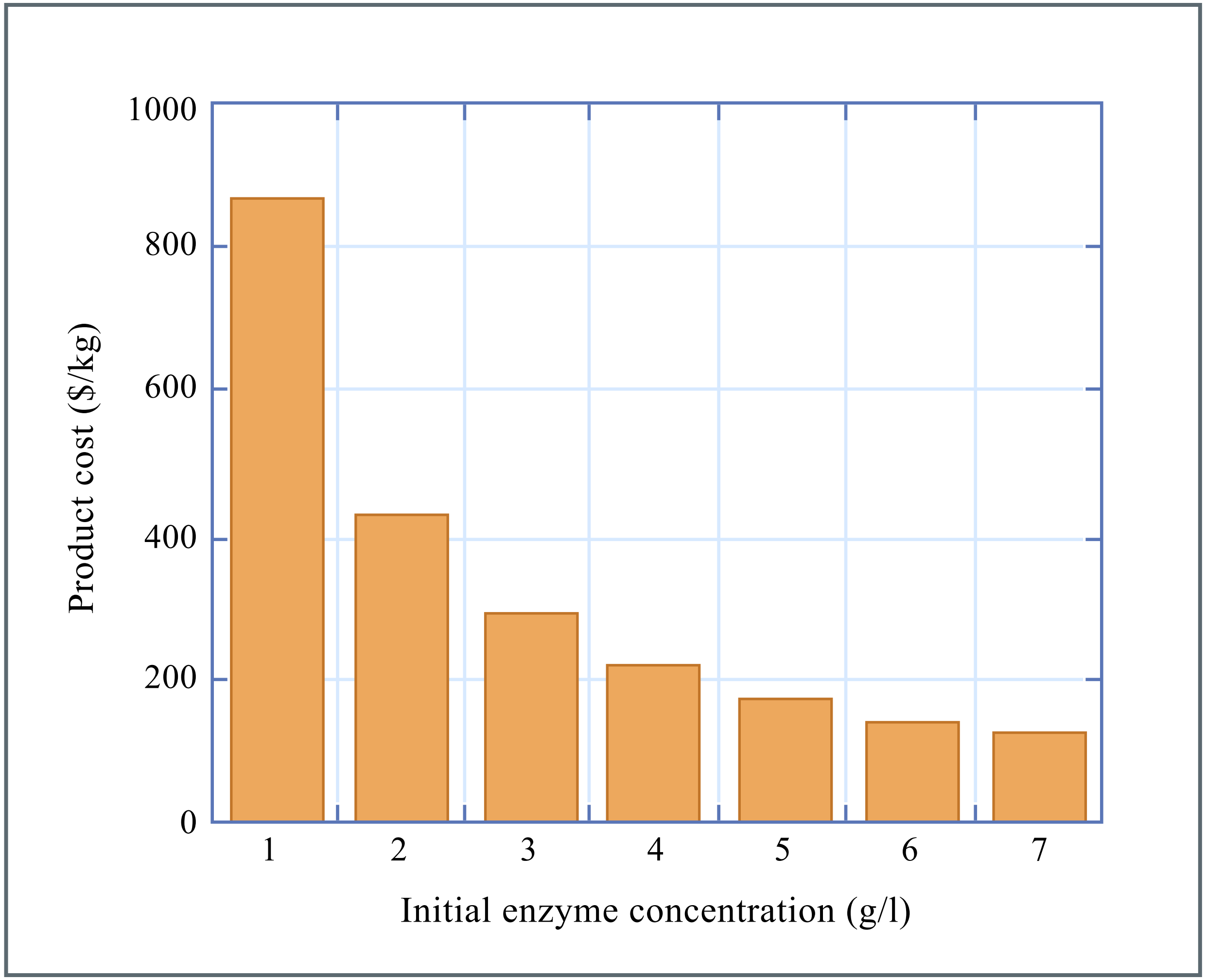


Figure by MIT OCW.

WHERE ARE THE PROBLEMS?

- **INADEQUATE <u>ANALYTICAL</u> TECHNIQUES**

- **SIMPLISTIC MODELS WITH <u>ASSUMPTIONS</u>**

- **<u>VARIANCE</u> IN SIGNALS AND PERFORMANCE**

- **INEFFICIENCIES IN <u>USE OF INFORMATION</u>**

- **INEFFICIENT <u>LEARNING</u>**