

# Batch Process Synthesis

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In the early stages of process design, especially when teaching undergraduates, it is recommended that several key steps be followed using heuristics rather than algorithmic approaches and optimization.

Until recently, the focus in process design was on the synthesis of processes to produce commodity chemicals, rather than specialty chemicals, including pharmaceuticals, in small quantities.

Recommendation – First introduce the synthesis steps for a commodity chemical process. Then, show that the steps are nearly identical for a batch process to produce specialty chemicals.



**Synthesis Steps**

<u>Synthesis Step</u>	<u>Process Operation</u>
• Eliminate differences in molecular types	Chemical reaction
• Distribute chemicals by matching <i>sources</i> and <i>sinks</i>	Mixing
• Eliminate differences in composition	Separation
• Eliminate differences in temperature, pressure and phase	Temperature, pressure and phase change
• Integrate tasks (combine <i>tasks</i> into <i>unit operations</i> )	

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### TISSUE PLASMINOGEN ACTIVATOR (tPA)

A recombinant, therapeutic protein  
- comprised of 562 amino acids

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**tPA activates plasminogen -**

to plasmin (an enzyme)

Plasmin dissolves fibrin formations that hold blood clots in place

Blood flow is re-established once the clot blockage dissolves -

important for patients with heart attacks (myocardial infarction) or stroke



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**tPA has been produced by Genentech (Activase™) since 1986**

Sells for \$2,000/100 mg dose

2003 - Patent protection expired

**Design objective -**

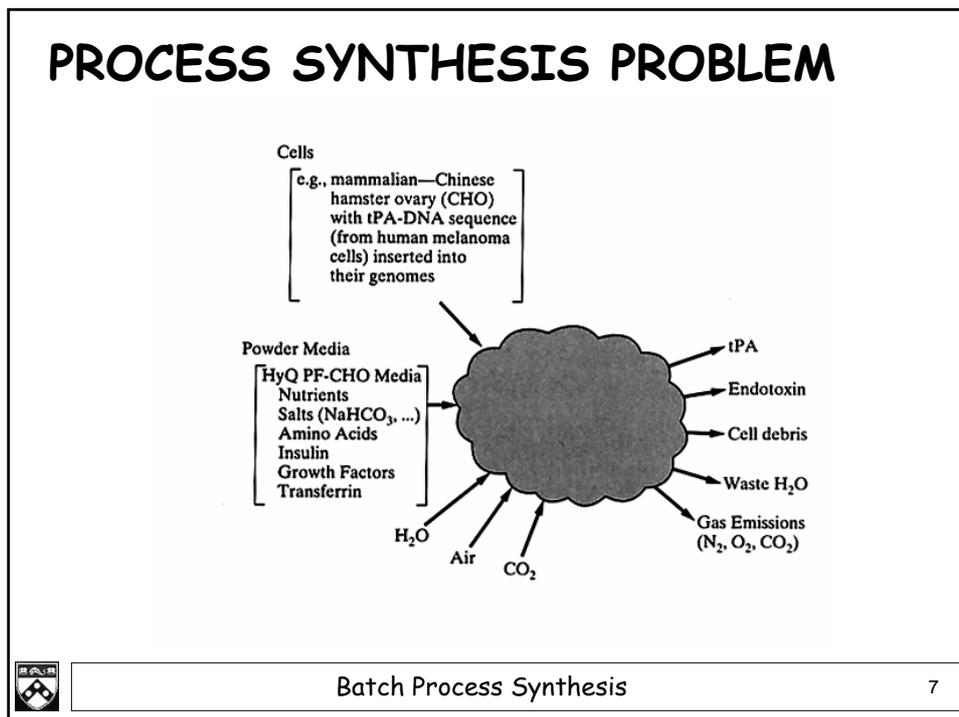
Manufacture generic form of tPA

Sell for \$200/dose



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### STEP 1. ELIMINATE DIFFERENCES IN MOLECULAR TYPE

**Identify Reaction Paths - with help from the Biochemist**

**1. Mammalian Cells**

tPA-DNA sequence + CHO cells → selected high expressing tPA-CHO cells (1)

(1-10 mg from human melanoma cells)	(10 <sup>6</sup> cells)	(CHO cells with tPA-DNA inserted in their genomes)
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Selected tPA-CHO cells ("founder cells") amplified to yield about 10<sup>6</sup> cells/mL - during R&D stage.  
These cells are frozen into 1-mL aliquots at - 70°C.

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**Master stock of tPA-CHO cells -**

Prepared in laboratory - stored in 1 mL aliquots at - 70°C

Used as inoculum for the bio-reaction:

**tPA-CHO cells + HyQ PF-CHO media + O<sub>2</sub> → Increased cell nos. (2)**

0.39×10<sup>6</sup> cells/mL-day  
50 pg tPA/cell-day  
0.2×10<sup>-12</sup> mol O<sub>2</sub>/cell-hr

Rates from Genentech patent (1988)

As tPA-CHO cells reproduce, tPA secretes into liquid media solution.

**SECOND REACTION PATH****2. Bacterial Cells**

**tPA-DNA sequence + E. coli cells → selected high expressing tPA-E. coli cells (3)**

Selected tPA-E. coli cells ("founder cells") amplified during R&D stage - frozen into 1-mL aliquots at - 70°C.

**tPA-E. coli cells + powder media + O<sub>2</sub> → increased cell nos. (4)**

Rate data not yet measured  
Cells may have to be "disrupted" to release tPA  
No patent exists



### INSERT REACTION OPERATIONS INTO FLOWSHEET

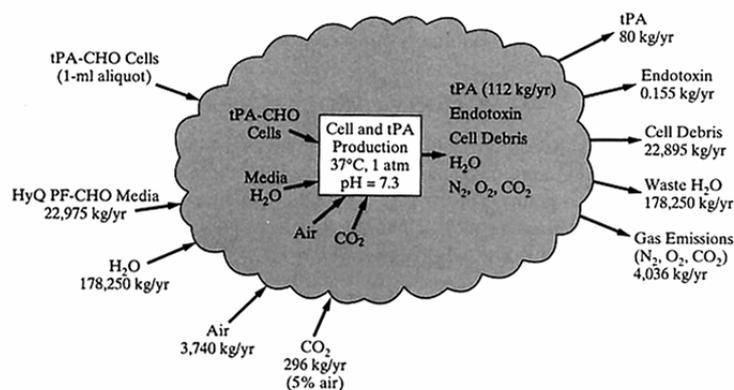


Figure 3.12 Reaction operations using mammalian CHO cells.



### EXAMINE GROSS PROFIT

Project cost of chemicals produced or sold

<u>Chemical</u>	<u>Kg/Kg tPA</u>	<u>Cost, \$/Kg</u>
tPA	1	2,000,000 <sup>x</sup>
HyQ PF CHO powder media	287.2	233
Water for injection (WFI)	2,228	0.12 <sup>+</sup>
Air	46.8	1,742
CO <sub>2</sub>	3.7	1,447
tPA-CHO cells	-	*

<sup>x</sup> \$200/100 mg dose

<sup>+</sup> \$0.45/gal = \$450/1,000 gal

\* Not included in gross profit estimate - related to cost of research, an operating cost.



### CALCULATE GROSS PROFIT

$$\text{Gross Profit} = 2,000,000 - 287.2 \times 233 - 2,228 \times 0.12 - 3.7 \times 1,447 - 46.8 \times 1,742$$

$$= \$1,846,000/\text{Kg tPA}$$

Does not include operating costs (cost of research and cost of utilities) and investment cost

- yet, high for a pharmaceutical

- process synthesis proceeds at an accelerated pace



### STEP 2: DISTRIBUTE THE CHEMICALS

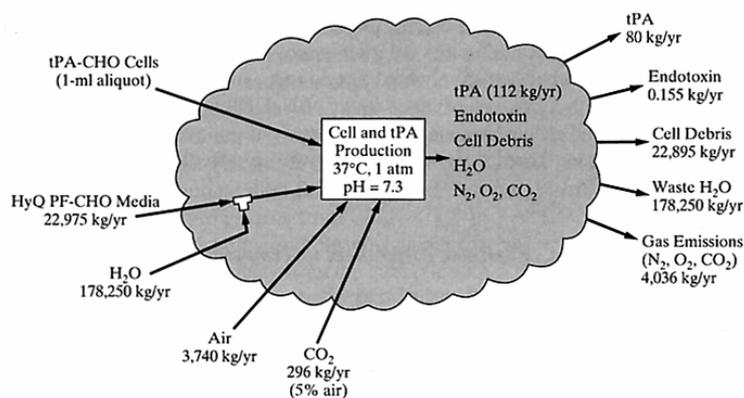
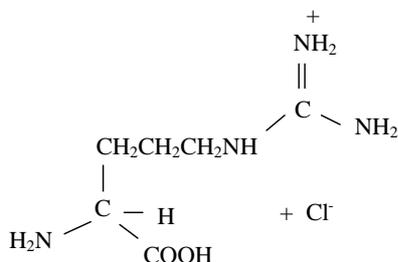


Figure 3.13 Flowsheet showing a distribution of chemicals for the tPA process.





**Arginine Hydrochloride - an amino acid**



prevents tPA from self-aggregating  
 After mixing, concentration is 2.0 M.

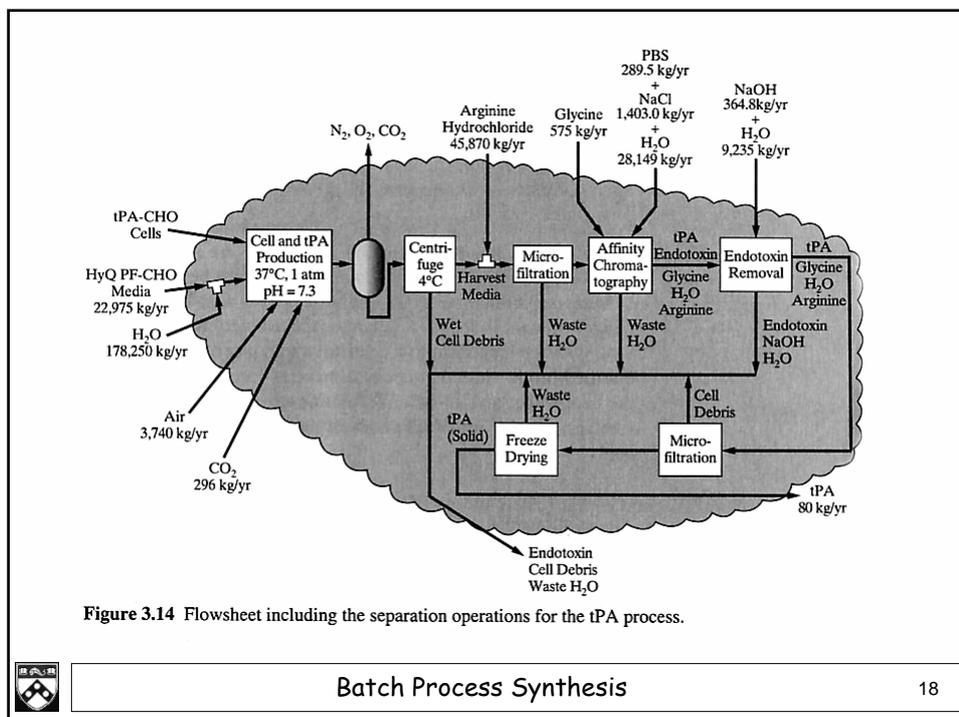
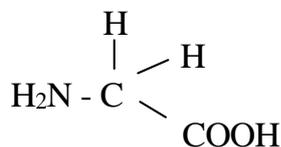


Figure 3.14 Flowsheet including the separation operations for the tPA process.



**Glycine** - Amino acetic acid



used to elute the affinity chromatography column

**Phosphate Buffer Solution (PBS)** - liquid medium for the equilibration of the affinity chromatography column

contains 0.65 M NaCl



**STEP 4. ELIMINATE DIFFERENCES IN TEMPERATURE**

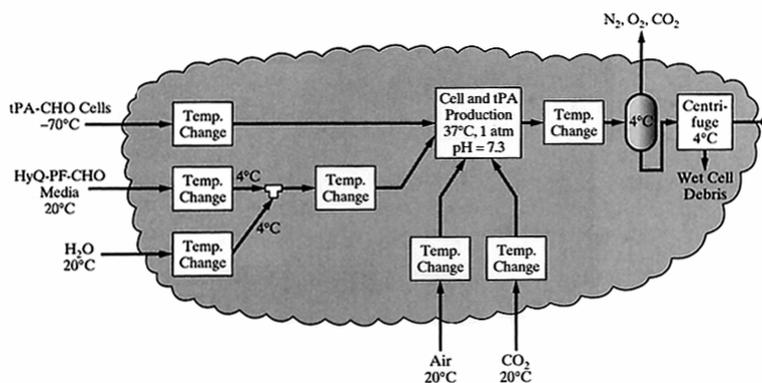


Figure 3.15 Flowsheet with the temperature-change operations in the tPA process.



## STEP 5. TASK INTEGRATION

Equipment items are selected - often combining operations into a single equipment item

Key decision - *batch* or *continuous* operation

80 Kg/yr tPA - batch mode

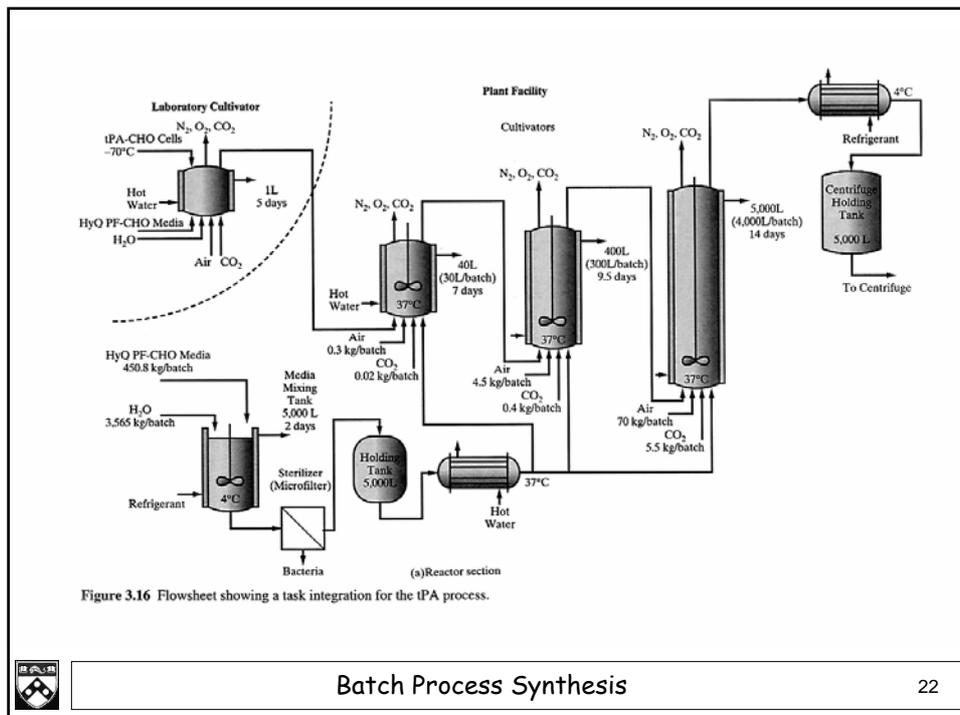
Select equipment sizes to produce 1.6 Kg/batch

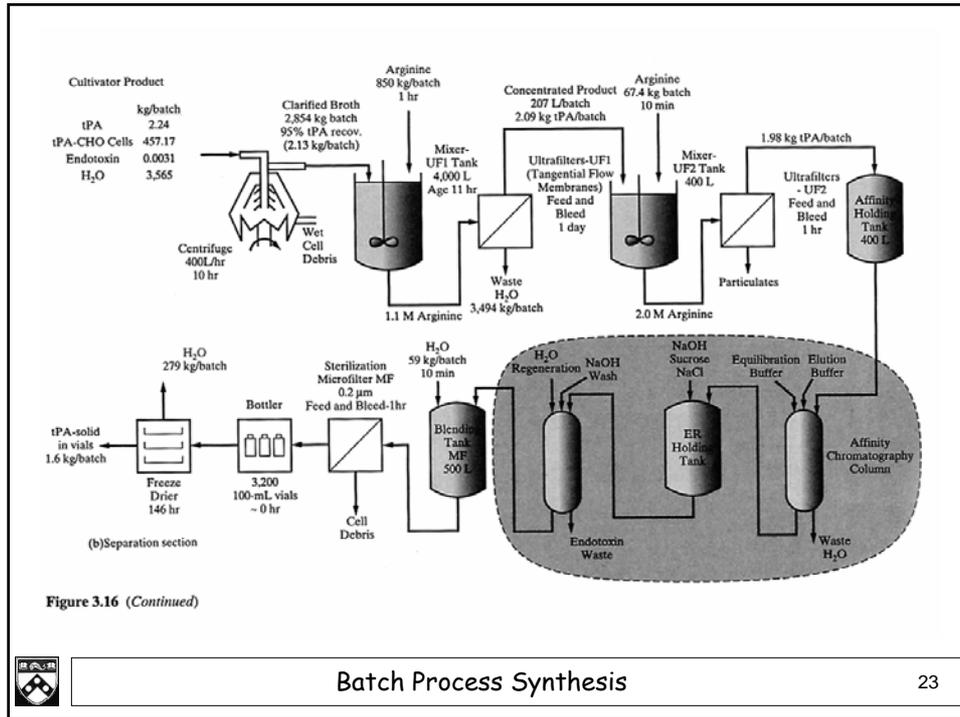
$$\text{i.e., } 80/1.6 = 50 \text{ batch/yr}$$

To allow for separation losses, produce 2.24 Kg/batch in the cultivators

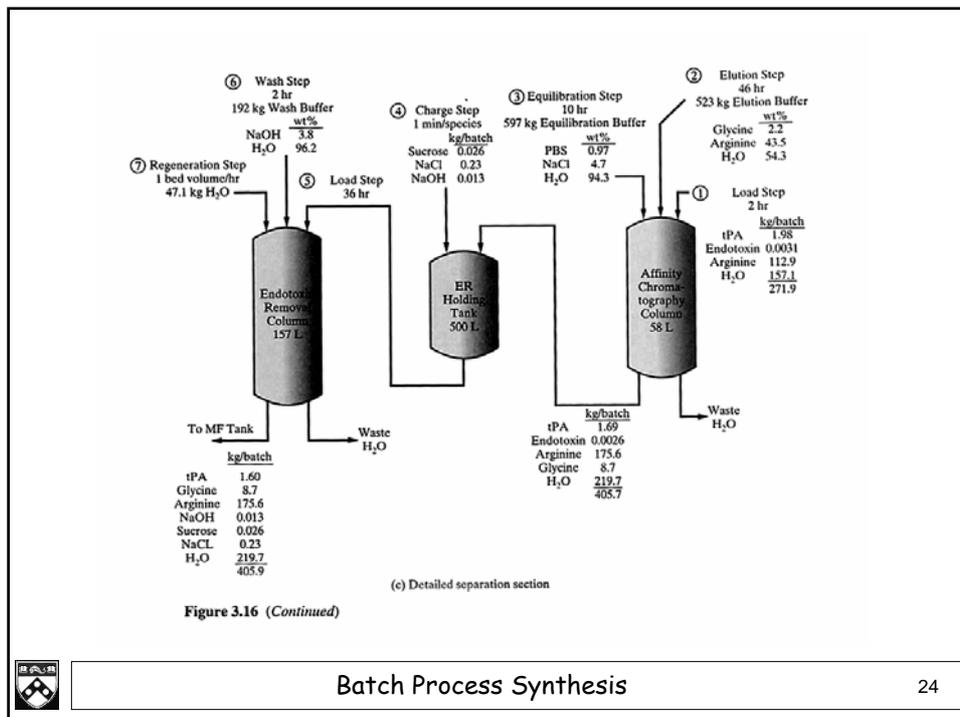
Using 5,000 L vessel, 14 day/batch = cycle time

Hence, run two batch trains in parallel - each producing 25 batch/yr

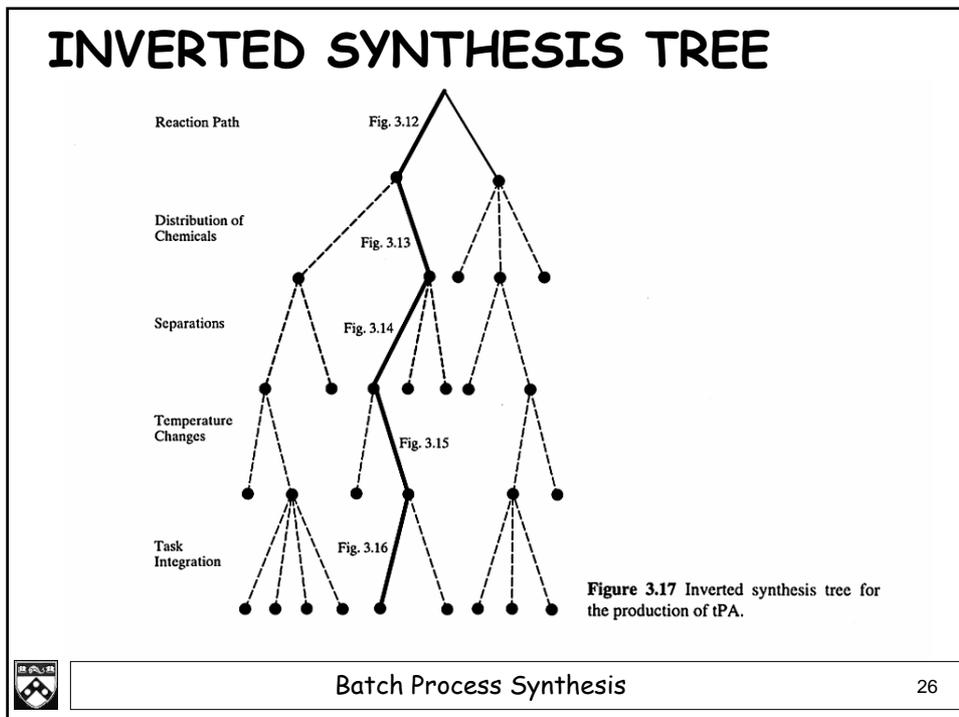
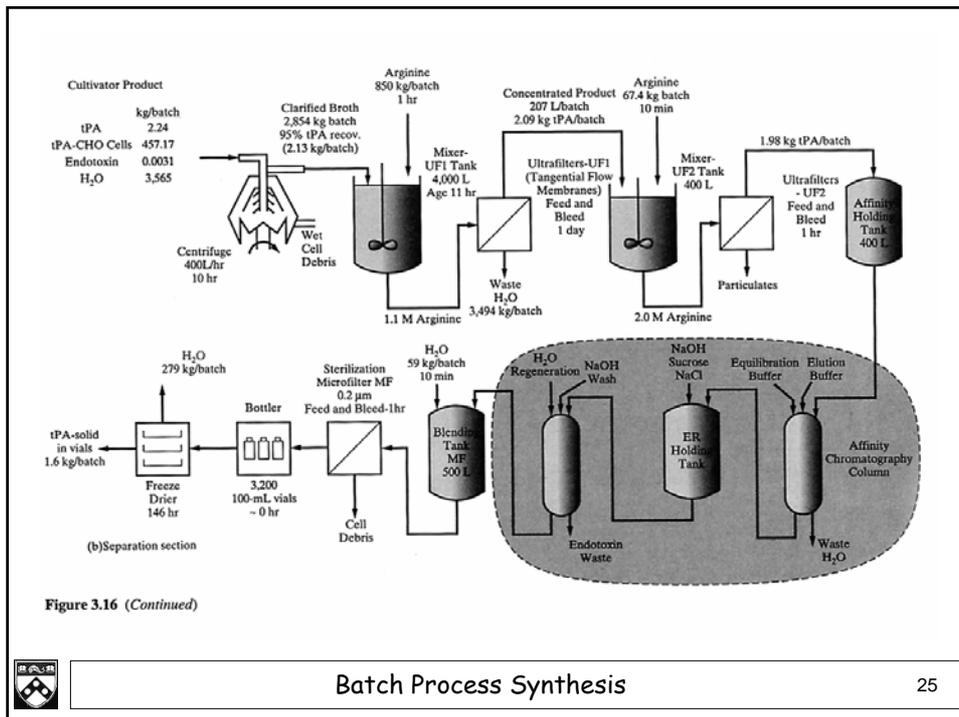




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### Simulation of Batch Processes

After process synthesis, given the process flowsheet and recipe of operations for each equipment item:

BATCH PLUS - Aspen Engineering Suite  
 SUPERPRO DESIGNER - Intelligen, Inc.

Carry out material and energy balances  
 Prepare operating schedule; i.e., Gantt chart

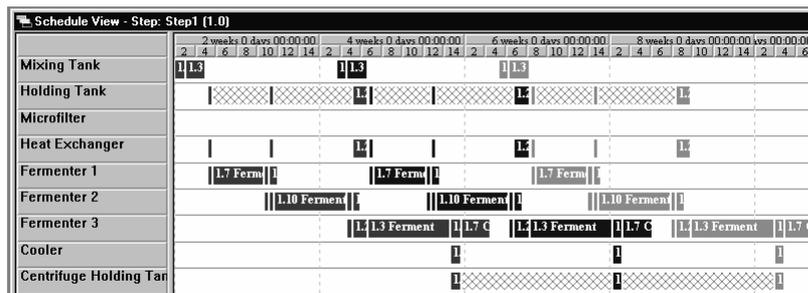
Equipment sized, costs estimated  
 and profitability analysis using  
 other software (e.g., Aspen IPE)

Design is adjusted to:

Reduce cycle time  
 Improve an economic objective



### Gantt Chart with Bottleneck



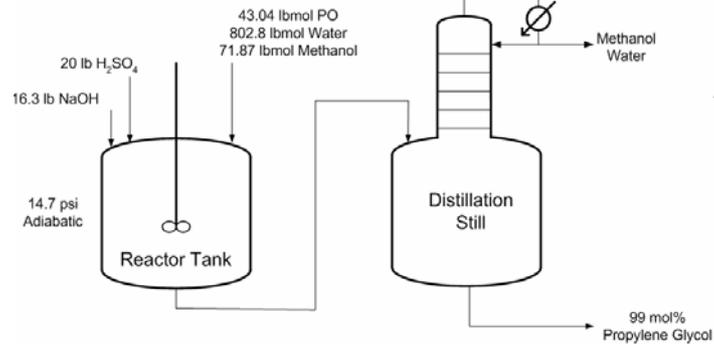
For a tutorial on the use of BATCH PLUS to simulate the tPA cultivator section, see the multimedia CD-ROM under ASPEN

For more comprehensive coverage in design courses, can focus on optimal sequences and schedules for batch operation.



### New Exercise Available

BATCH PLUS simulation of batch process to produce propylene glycol by hydrolysis of propylene oxide.



See problem statement and solution in the file, **Batch Manufacture of Propylene Glycol.pdf**, on the workshop web site.

A multimedia tutorial on the BATCH PLUS solution is available on the multimedia CD-ROM under ASPEN PLUS.

