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.

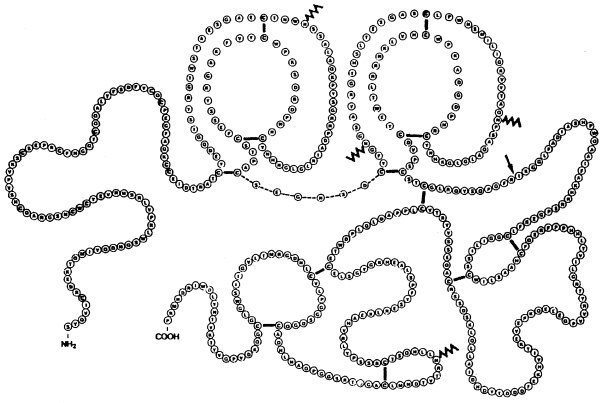
> Recommendation – First introduce the synthesis steps for a commodity chemical process. Then, show that the steps are nearly identical for a batch process to produce specialty chemicals.

Synthesis Steps

Synthesis Step	Process Operation
1. Eliminate differences in molecular types	Chemical reaction
2. Distribute chemicals by matching *sources* and *sinks*	Mixing
3. Eliminate differences in composition	Separation
4. Eliminate differences in temperature, pressure and phase	Temperature, pressure and phase change
5. Integrate tasks (combine *tasks* into *unit operations*)	

TISSUE PLASMINOGEN ACTIVATOR (tPA)

A recombinant, therapeutic protein
- comprised of 562 amino acids



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

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

Sells for $2,000/100 mg dose

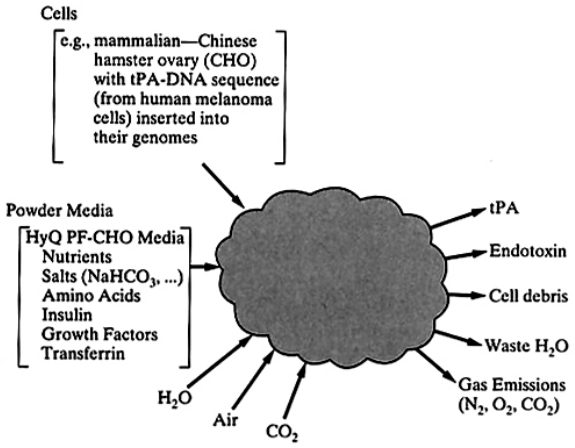
2003 – Patent protection expired

Design objective –

Manufacture generic form of tPA

Sell for $200/dose

PROCESS SYNTHESIS PROBLEM



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) (10^6 cells) (CHO cells with tPA-DNA inserted in their genomes)

Selected tPA-CHO cells ("founder cells") amplified to yield about 10^6 cells/mL – during R&D stage.
These cells are frozen into 1-mL aliquots at - 70°C.

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_2 → Increased cell nos. **(2)**

0.39×10^6 cells/mL-day
50 pg tPA/cell-day
0.2×10^{-12} mol O_2/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_2 → 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

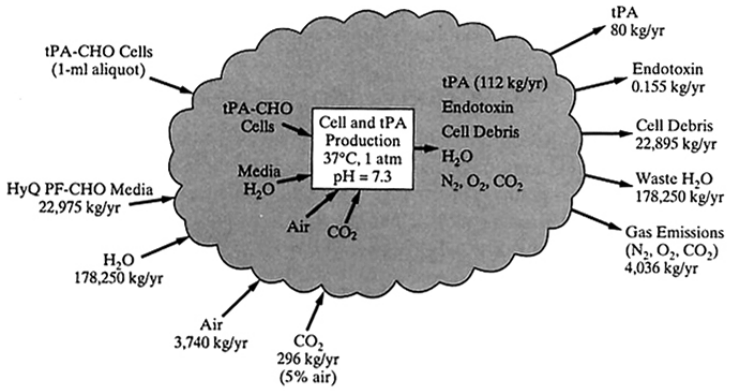


Figure 3.12 Reaction operations using mammalian CHO cells.

EXAMINE GROSS PROFIT

Project cost of chemicals produced or sold

Chemical	Kg/Kg tPA	Cost, $/Kg
tPA	1	2,000,000×
HyQ PF CHO powder media	287.2	233
Water for injection (WFI)	2,228	0.12+
Air	46.8	1,742
CO_2	3.7	1,447
tPA-CHO cells	-	*

× $200/100 mg dose
+ $0.45/gal = $450/1,000 gal
* Not included in gross profit estimate – related to cost of research, an operating cost.

CALCULATE GROSS PROFIT

Gross Profit = 2,000,000 – 287.2×233 – 2,228 ×0.12
-3.7 ×1,447 – 46.8 ×1,742

= $1,846,000/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

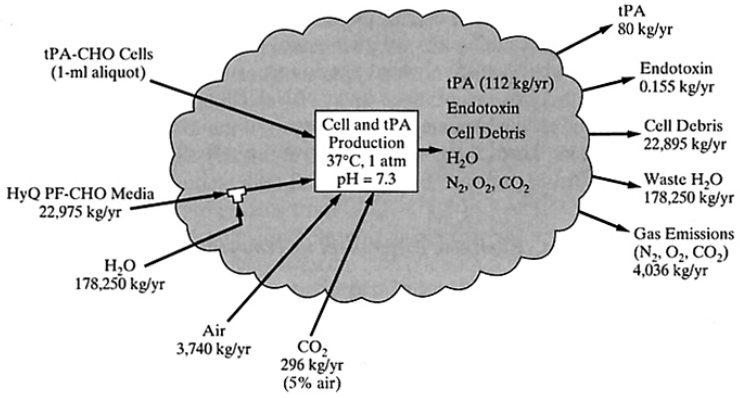


Figure 3.13 Flowsheet showing a distribution of chemicals for the tPA process.

STEP 3: ELIMINATE DIFFERENCES IN COMPOSITION

tPA protein must be recovered from other proteins, cell debris, media, water, and gas emissions

Proteins lose activity (denature) at temperatures above ~ 0°C

Hence - entire separation process designed to operate at 4°C, slightly above freezing point of water.

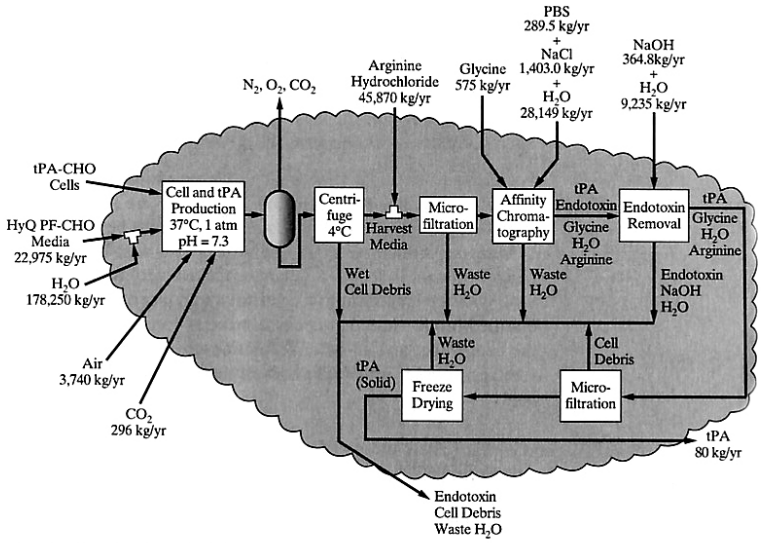
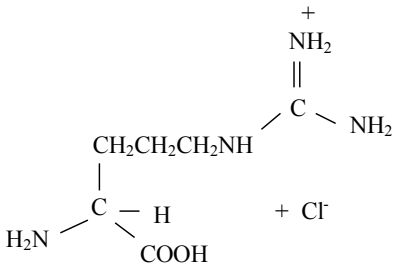


Figure 3.14 Flowsheet including the separation operations for the tPA process.

Arginine Hydrochloride – an amino acid



prevents tPA from self-aggregating

After mixing, concentration is 2.0 M.

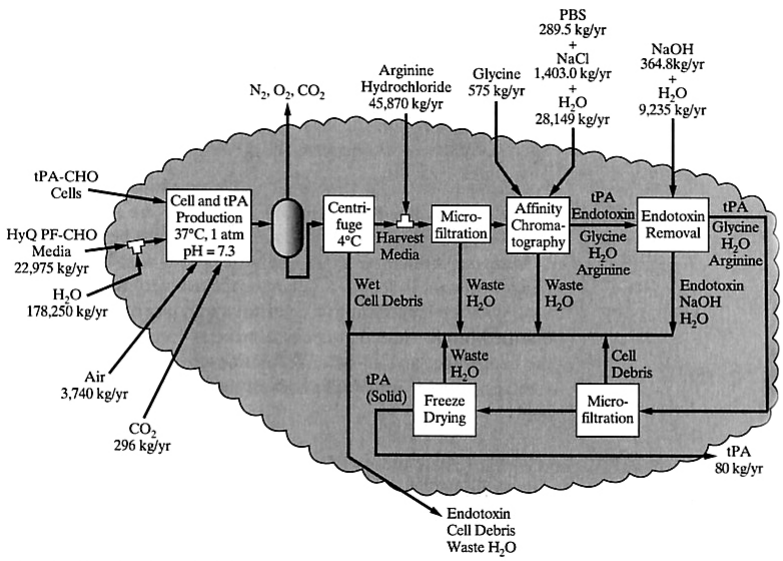
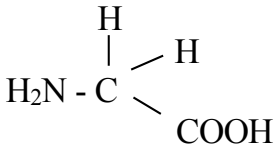


Figure 3.14 Flowsheet including the separation operations for the tPA process.

Glycine – Amino acetic acid



used to elute the affinity chromotagraphy column

Phosphate Buffer Solution (PBS) – liquid medium for the equilibration of the affinity chromotagraphy column

contains 0.65 M NaCl

STEP 4. ELIMINATE DIFFERENCES IN TEMPERATURE

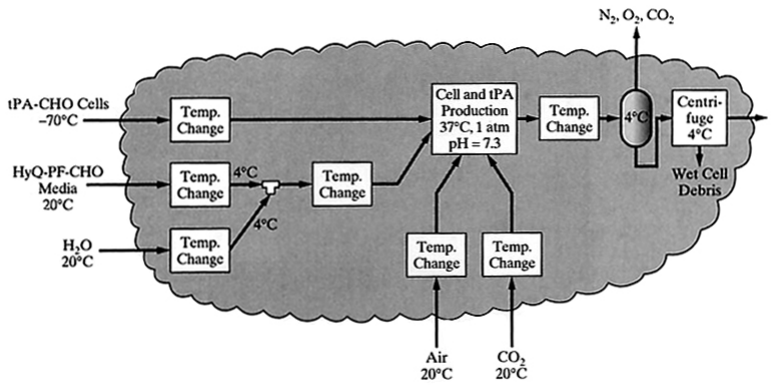


Figure 3.15 Flowsheet with the temperature-change operations in the tPA process.

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

i.e., 80/1.6 = 50 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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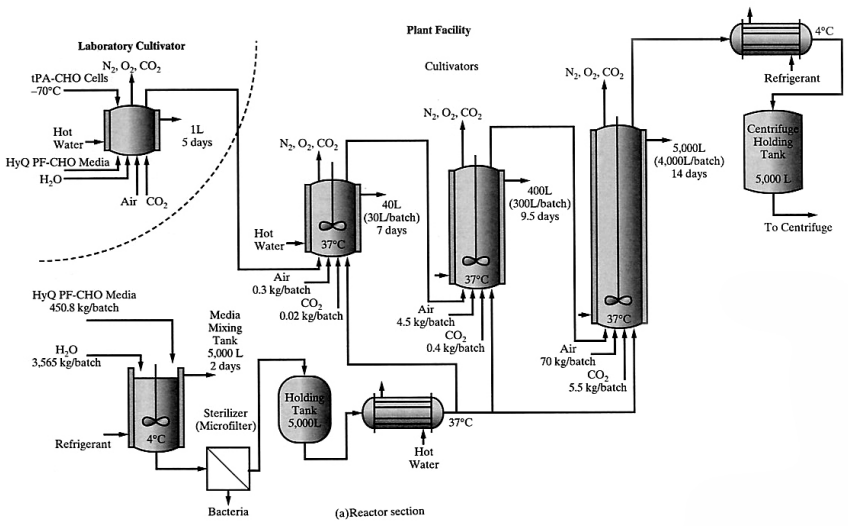

Figure 3.16 Flowsheet showing a task integration for the tPA process.

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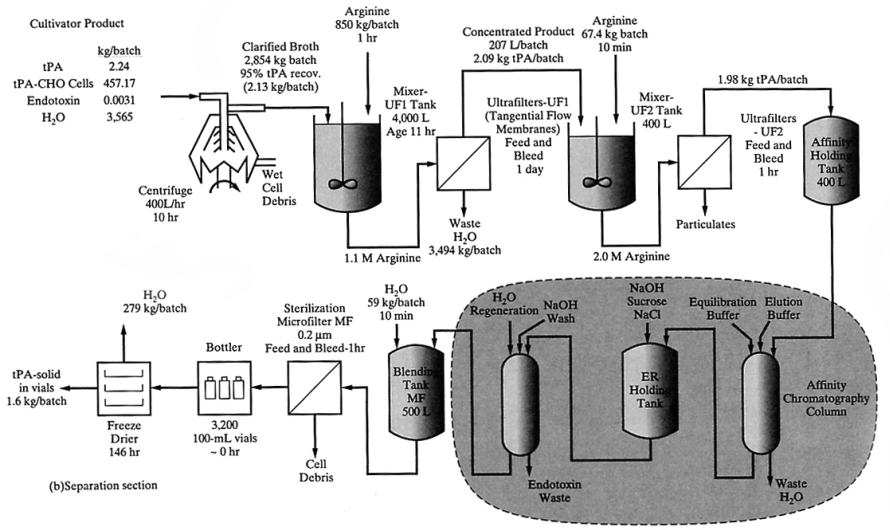

Figure 3.16 (*Continued*)

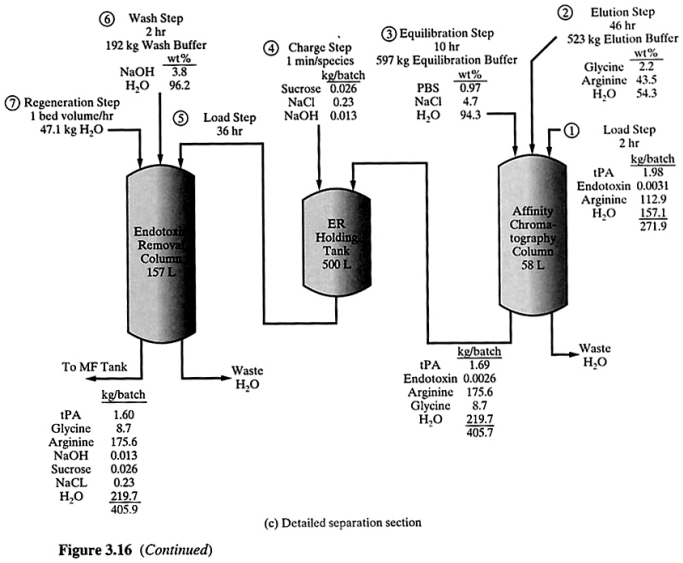

Figure 3.16 (*Continued*)

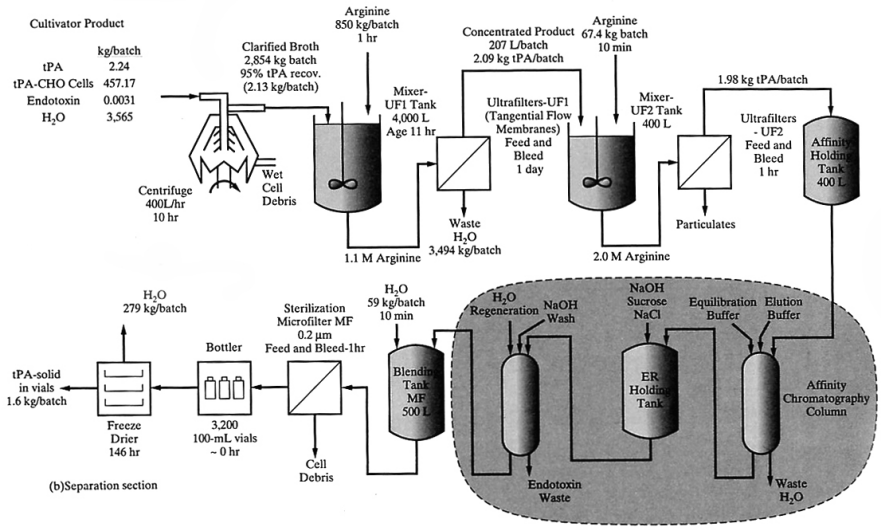

Figure 3.16 (*Continued*)

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INVERTED SYNTHESIS TREE

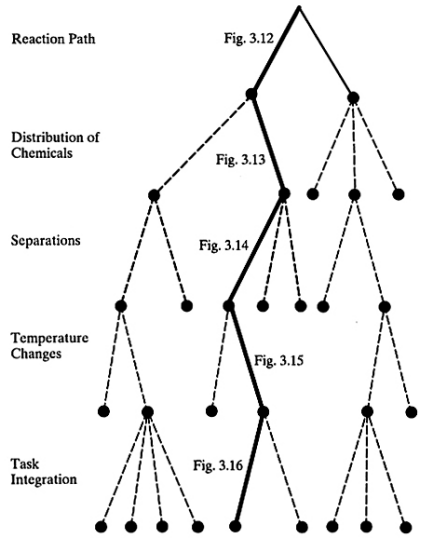

Figure 3.17 Inverted synthesis tree for the production of tPA.

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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.

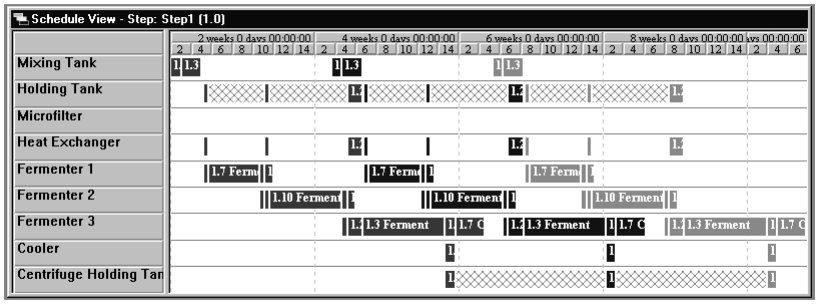
Carry out material and energy balances
Prepare operating schedule; i.e., Gantt chart

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

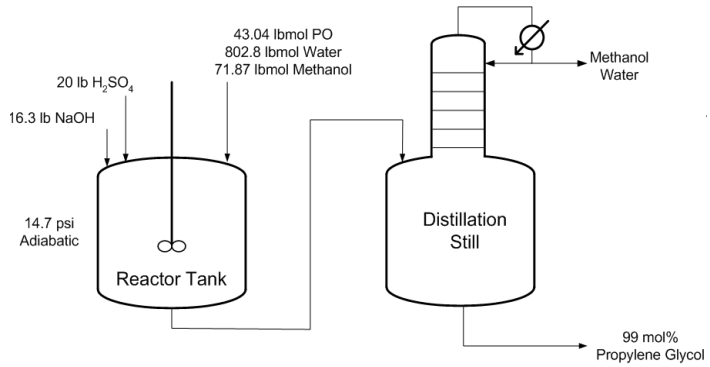
Gantt Chart with Bottleneck



For 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 tutorial on the BATCH PLUS solution will be added to the next edition of our multimedia.

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