Using Batch Process Simulation to Increase Throughput in Biopharmaceutical Facilities

TECHNICAL PAPER

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Batch process simulation represents the critical components of an entire manufacturing process through a computer model. Examples of an overall process model are shown in Figures 1 and 2. This malleable model can:

- Perform component-level material and energy balances
- Determine appropriate equipment size
- Calculate utility demand as a function of time
- Estimate the time frame for a complete process cycle
- Identify capital costs and cost of goods
- Evaluate environmental impact
- Establish raw material usage
- Quantify key performance indicators (throughput or capacity)

Figure 1: Overall Facility and Process Model

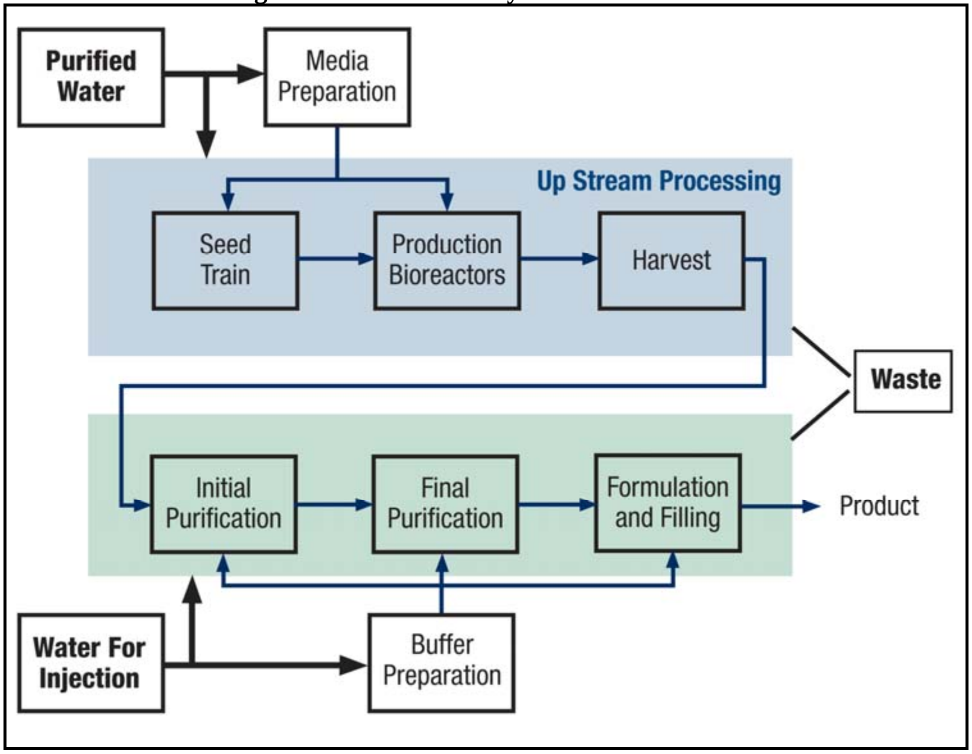
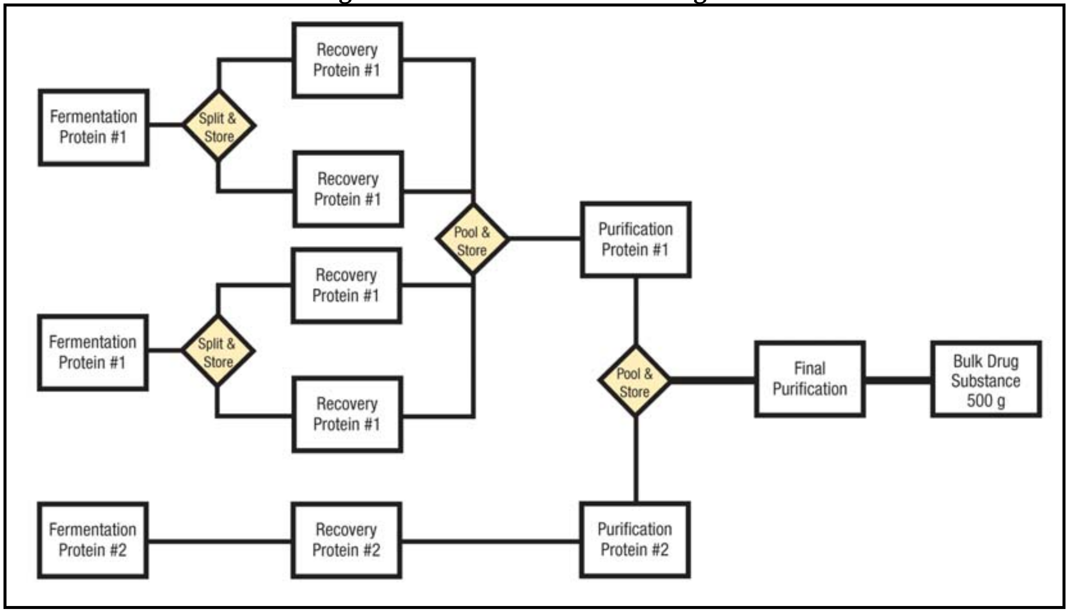
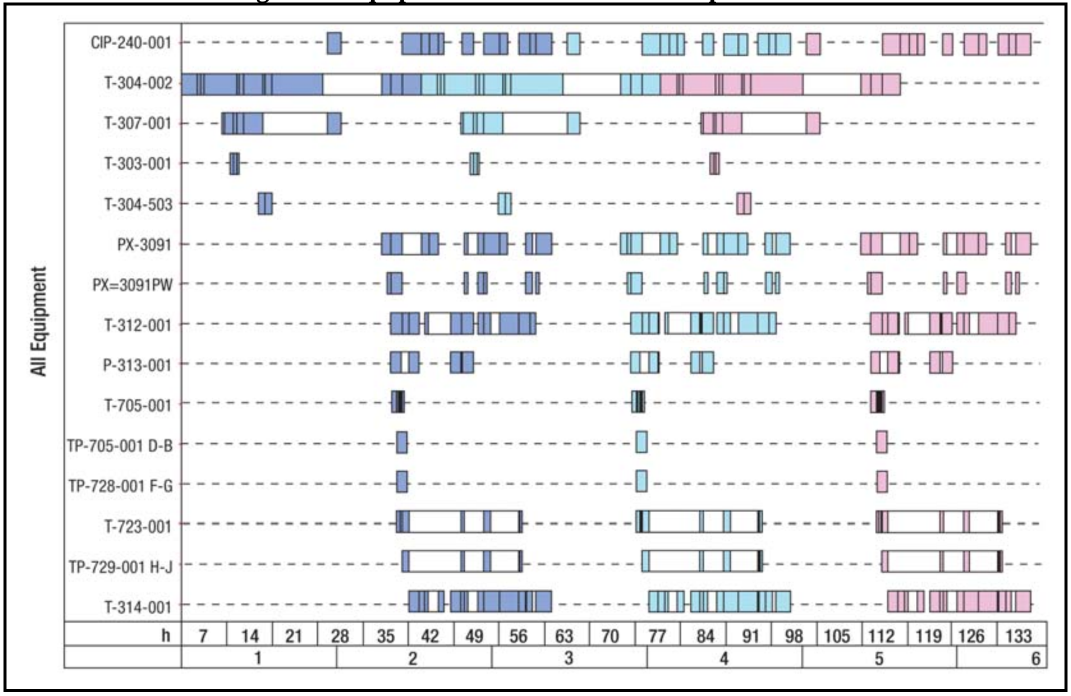


Figure 2: Process Block Flow Diagram



For the biopharmaceutical industry, batch process simulation can yield realistic predictions with its ability to model multiple processes, even those that share unit operations (see Figure 3). Batch process simulation for biopharmaceutical facilities can optimize capital investments, assure capacity needs, manage operational costs, provide design-basis documentation, evaluate alternatives, facilitate technology transfer, and enable interdisciplinary and interdepartmental communication.

Figure 3: Equipment Utilization for Multiple Batches



The following outlines three theoretical case studies that illustrate how batch process simulation can model the current state of a biopharmaceutical process, the same process with incremental improvements and the same process with major facility changes.

CASE 1: CURRENT STATE

Evaluation

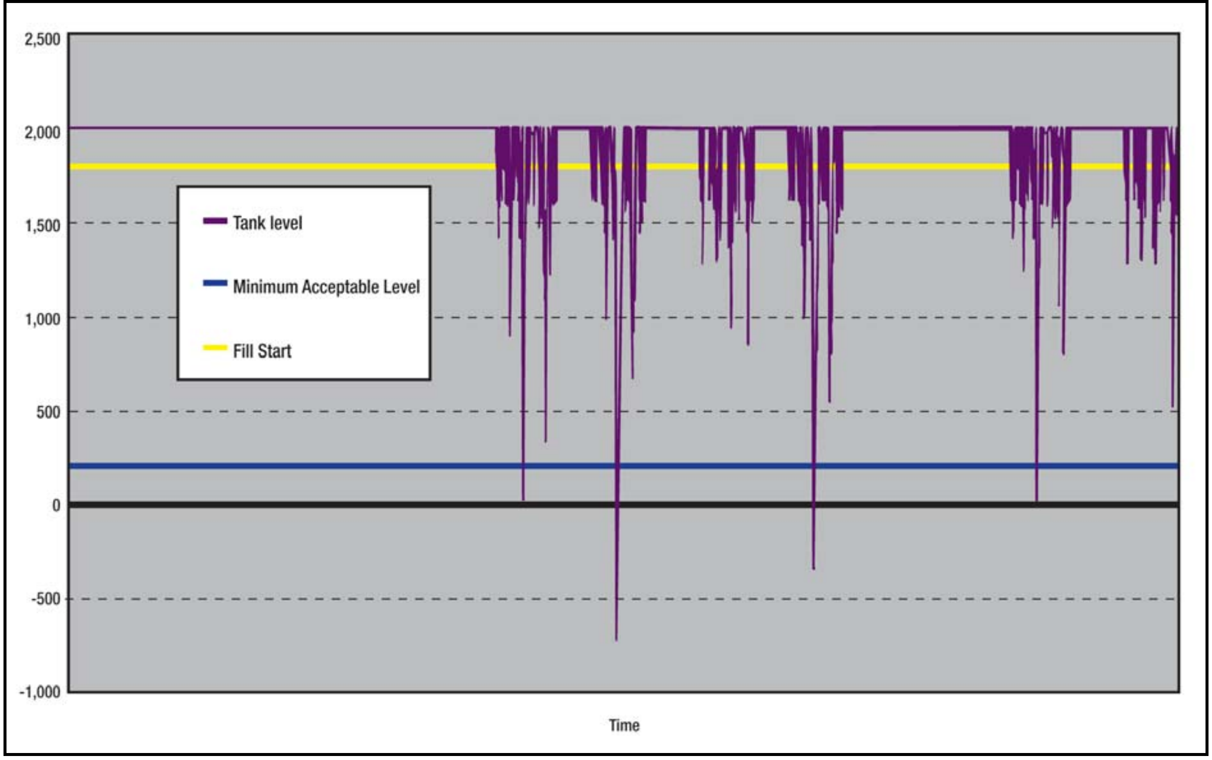
How much can be theoretically produced with existing equipment and staff?

- Sequential operation of process to complete one cycle by one staff
- Pre-owned facility and equipment validated for new process
- Existing/available equipment used for unit operations

Performance Indicators

- Throughput = 250 grams/month
- Sufficient purified water (PW) generation, storage and distribution
- Insufficient water for injection (WFI) generation and storage
    - WFI constraints caused self-imposed delays in operations (see Figure 4)
- Some waste streams must be segregated to achieve throughput

Figure 4: Insufficient WFI Capacity



CASE 2: INCREMENTAL IMPROVEMENTS

Evaluation

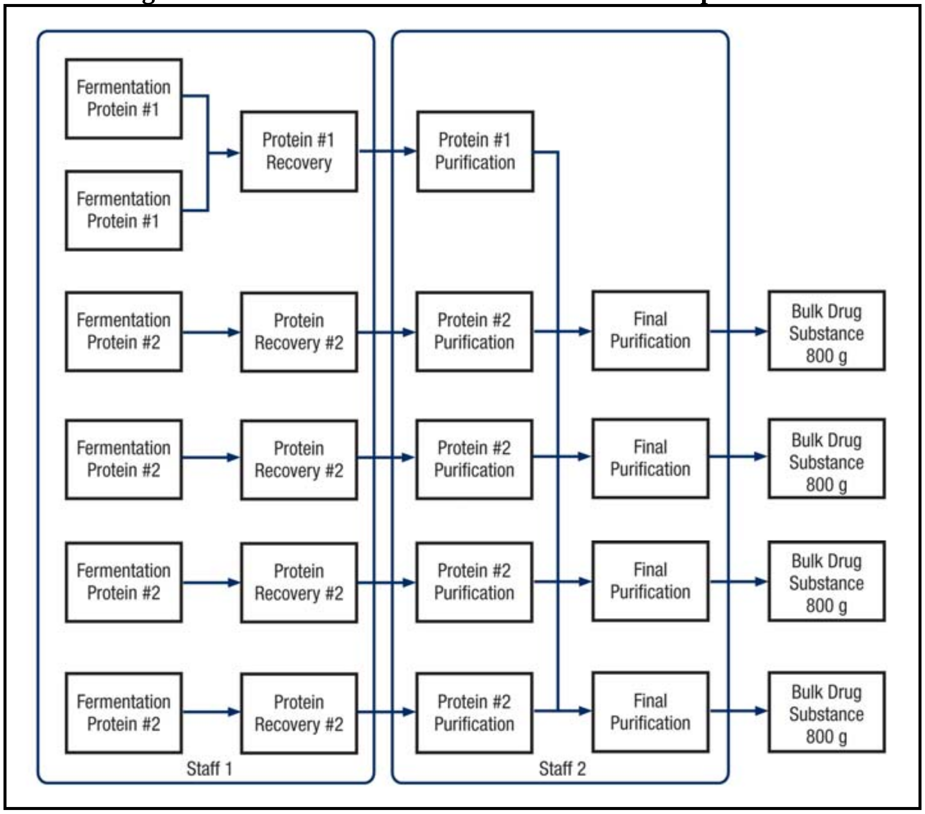
How much can be theoretically produced with an incremental investment in equipment and staff and incremental improvements in process?

- Process improvements
  - Increase titer due to fermentation improvements
  - Minor modifications to recovery steps due to process development projects
- Additional equipment
  - Minor capital investment in WFI storage tank
- Doubling of staff (see Figure 5) allows parallel operation of upstream and downstream processing

Performance Indicators

- Throughput = 400 grams/month, a 60% increase in production over case 1
- Sufficient PW generation and storage
- Sufficient WFI generation and storage
  - WFI storage tank is installed
- Some waste streams must be segregated
- Staff utilization
  - Staff 1: 77% utilized
  - Staff 2: 80% utilized
- Purification suite bottleneck
- Fermentation and recovery rescheduled to manage water and waste

Figure 5: Double Staff Size Allows Some Parallel Operations



CASE 3: MAJOR FACILITY CHANGES

Evaluation

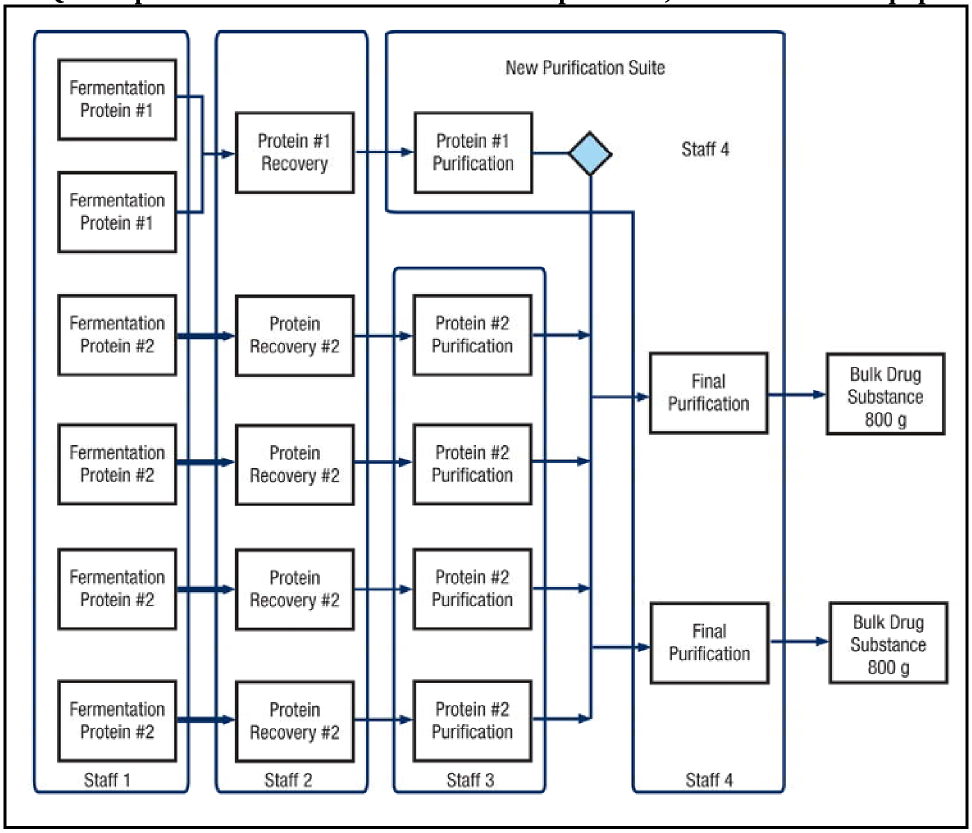
How much can be theoretically produced with a significant investment in equipment, facility and staff and continued incremental improvements in process?

- Increase size of final purification equipment
- Reconfigure facility to add:
  - New purification suite
  - New prep and hold equipment
  - New recovery equipment
- Parallel operation of upstream and downstream processing allowed
  - Staff quadrupled (see Figure 6)

Performance Indicators

- Throughput = 800 grams/month, an 100% increase over case 2 and 220% increase over case 1
- Pressed limits of PW generation and storage for this throughput
- Pressed limits of WFI generation and storage for this throughput
- Some waste streams must be segregated
- Staff utilization
  - Staff 1: 77% utilized
  - Staff 2: 50% utilized
  - Staff 3: 53% utilized
  - Staff 4: 56% utilized

Figure 6: Quadruple Staff Size Allows Some Parallel Operations, Additional New Equipment



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CONCLUSION

Batch process simulation can be used to study increase in throughput and reveal facility constraints and limits to production capacity. Strategically removing facility constraints can lead to additional throughput with minor investments. Increases in throughput due to major facility renovations and significant changes to staffing levels can also be quantified using batch process simulation.

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