BATCH PROCESS SIMULATION TOOLS FOR BIOPROCESSING

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Merrick has been engineering projects in the industrial bioprocessing industry for more than 25 years. In that time, we've seen the industry expand to include alternative proteins and sustainable foods, in addition to biofuels and biochemicals. Many of these bioprocessing technologies employ batch processing operations, such as fermentation, as opposed to continuous chemical processing systems. Batch operations require a more holistic approach when designing equipment and systems, therefore demanding more thorough process engineering analysis than similar continuous operations.

To meet the demand for a more thorough analysis, process simulation tools are used to develop rigorous mass and energy balances (MEBs) needed for process design. The output of these MEBs enables the specification of equipment and identification of the number of operating trains, thereby allowing for a Total Installed Cost (TIC) estimate to be developed for the project. Developing a reliable TIC estimate early in Front End Engineering Design (FEED, also known as Front End Loading, or FEL) reduces the risk of making capital cost related design changes later in the design process.

Figure 1: Commercial Fermentation Facility

Simulation software platforms provided by AspenTech are state-of-the-art for the chemical processing industry. Traditionally, Aspen Plus has been used in the bioprocessing industry to model emerging technologies such as the conversion of lignocellulosic biomass to hydrocarbon fuels . Aspen Plus and Aspen HYSYS can be used to model batch processing systems as pseudo-continuous models by time-averaging non-continuous flowrates. The output of these continuous models must then be translated into batch capacities and equipment schedules using external spreadsheet programs. This type of modeling can be used to develop the design for food-grade fermentation processes like the example process depicted in *Figure 2*.

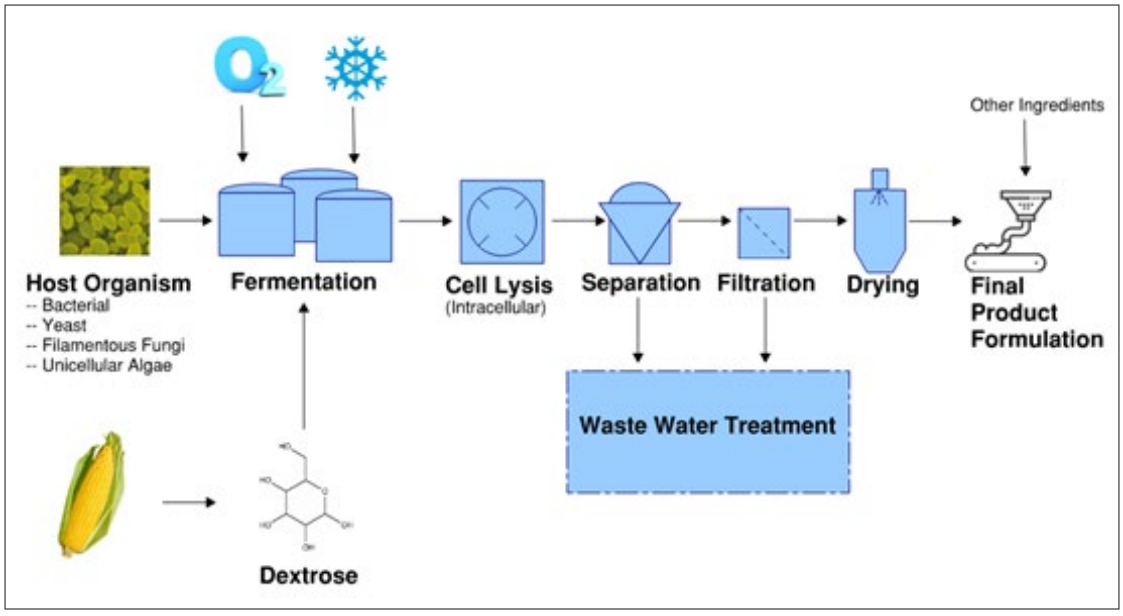

Figure 2: Example Fermentation Process Schematic

Other process modeling tools such as SuperPro Designer and Aspen Batch Process Developer have been developed specifically to model batch processing systems. The SuperPro and SchedulePro simulation programs developed by Intelligen, Inc. are used extensively in the biotechnology, pharmaceutical, specialty chemicals, and food industries.

- SuperPro has the capability to model both continuous and batch processes and to interface between continuous and batch.
- SchedulePro is a capacity scheduling tool for batch and semi-continuous manufacturing processes.

These modeling platforms can be used to expedite the development of MEBs and cost estimates for early-stage bioprocessing design projects. The level of rigor required by the simulation and resulting MEBs may differ with various stages of the FEL process.

BATCH SIMULATION FOR FEL2

As part of an FEL2 design package for many commercial bioprocessing projects, a Class 4/3 cost estimate with a typical accuracy of +/-30 is first developed, as defined by the Association for Advancement of Cost Engineering (AACE). For an FEL2 level cost estimate, the process simulation must define flow rates and conditions for all major process streams and utilities so major equipment can be sized and estimated. This can be achieved using either of the simulation methods previously discussed: by developing a pseudo-continuous model using Aspen Plus or by using batch simulation software. Either option provides the fundamental tools required for chemical process calculations:

- chemical component databases;
- VLE separations modules; and
- kinetic reaction modeling.

For fermentation systems, however, thermodynamically rigorous reaction modeling may not always be warranted. Bioreactors can be modeled using empirically derived conversions for specific reactions, such as the conversion of glucose to a target protein. Especially for early-stage newly developed projects, rigorous kinetics or rate expressions may not be available. In these cases, simple stoichiometric models can often satisfy the MEBs needed for FEL2 cost estimates.

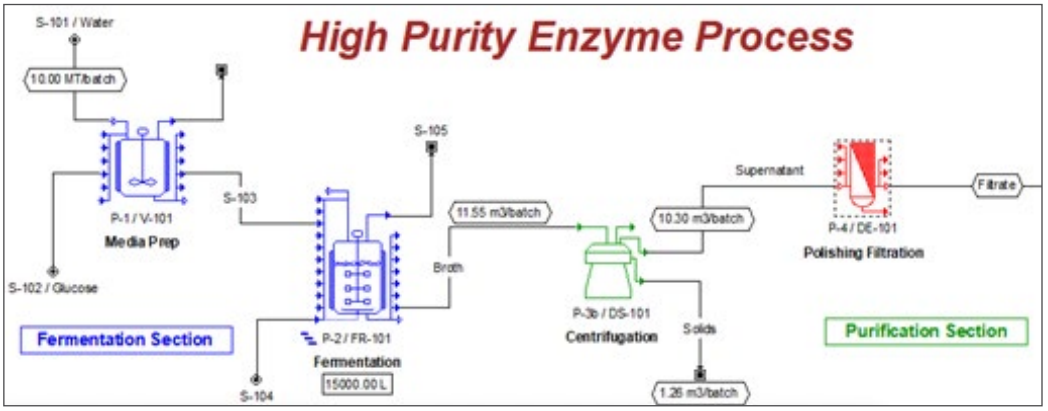

Figure 3: Fermentation Process Flowsheet (SuperPro)

A bioprocess simulation starts with the development of a process flowsheet for the production, recovery, and purification of the biological product of interest. A simplified SuperPro flowsheet for a generic fermentation process is shown in *Figure 3*. Input data for the simulation is typically supplied using prior results from the laboratory, pilot plant, or contract manufacturing facility. From this data, inputs such as capacity; compositions; operating conditions; heating/cooling requirements; processing time; and yields or other performance parameters for each unit operation are determined and specified in the simulation.

In general, these inputs are no different than those for a continuous simulation. However, each unit operation in a batch process may have multiple operating steps. For example, a typical production fermenter (represented by P2/FR-101 in Figure 3) can have a batch schedule with the following sequential steps:

1. Steam in place (SIP)
2. Media transfer in
3. Glucose transfer in
4. Inoculation
5. Growth
6. Production/Fed batch
7. Transfer out
8. Clean in place (CIP)
9. Idle

Each of these steps has its own sets of inputs: performance parameters; operating conditions; and processing time. For example, the user may specify that during Step 7, 11.5 cubic meters of fermentation broth transfers out in 1.25 hours. Once the mass of each stream for a batch operating step is calculated, an overall material balance for the major flow streams can be determined. A simplified stream table for a single fermentation batch and separation step is shown in *Figure 4*.

	Media	Glucose	Fermentation Broth	Solids	Supernatant	Filtrate
Stream Properties						
Batch Mass (kg/batch)	10,000	1,000	11,582	1,274	10,308	10,300
Temperature (°C)	25.0	25.0	15.0	18.0	18.0	18.0
Pressure (bar)	1.103	1.103	0.916	0.916	0.916	0.916
Volume (L/batch)	10,053	852	11,554	1,265	10,301	10,294
Component Mass (kg/batch)						
Biomass	0	0	194.0	190.1	3.88	0
Glucose	0	1,000	30.0	2.86	27.1	27.1
Media Components	500	0	0	0	0	0
Impurities	0	0	48.5	4.62	43.9	43.9
Protein	0	0	97.0	9.23	87.8	87.7
Water	9,500	0	11,213	1,068	10,145	10,141

Figure 4: Fermentation Stream Table

An equipment schedule and energy balance must be developed in conjunction with the resulting material balance. For example, the total time in the fermentation production phase and the heat generated during this phase must be specified so the required cooling duty can be calculated. This allows for demands on utilities such as chilled water systems to be determined so that the utility equipment can be sized and estimated. Steam needed for SIP and chemicals used for CIP also must be quantified.

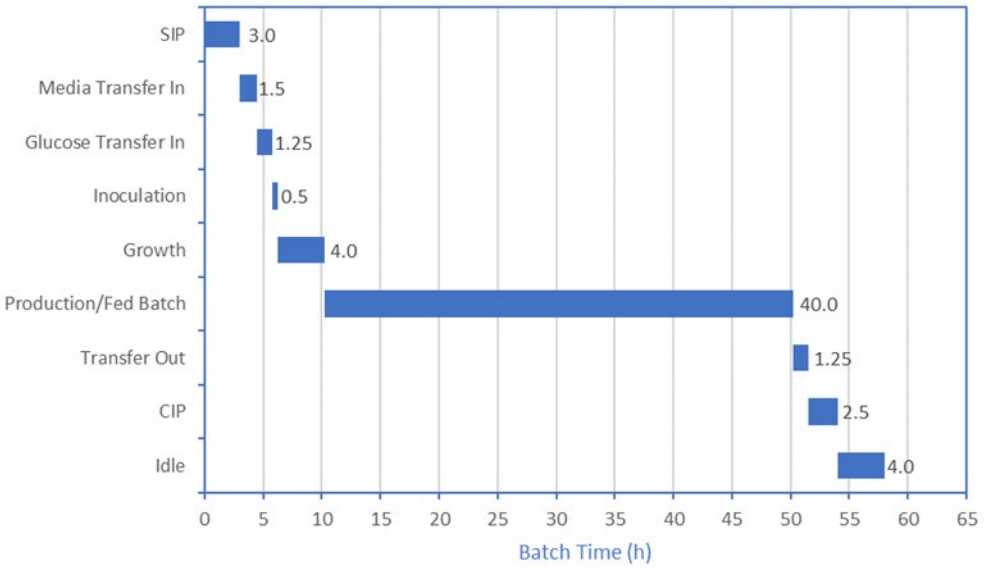

Figure 5: Gantt Chart for a Single Production Fermenter Batch

In batch modeling programs such as SuperPro, batch schedules and energy balances can be manipulated directly in the simulation, or the data can be exported to excel spreadsheets for manual calculations. An example of a Gantt chart showing the batch schedule for an individual batch of the fermentation process described above is shown in *Figure 5*. This batch schedule shows that each fermenter will be sterilized, operated, cleaned, and turned around for a subsequent batch every 58 hours. Gantt charts allow the simulation user to visualize the schedule for a batch process and assess whether the duration and sequence of operating steps are specified appropriately.

For equipment to be sized for batch operations, the instantaneous flowrate must be determined for each operating step. For the example fermentation depicted in the Figure 5 Gantt chart, each operating step that requires the transfer of material from one unit operation to another will have a time-averaged flowrate across the 58 hours of the entire fermenter cycle (the output of a time-averaged continuous simulation). In a batch simulation, the instantaneous flowrate for each operating step is calculated, as shown in *Figure 6*. The results show that the fermentation broth transfer pump needs to be designed for a capacity of 9,266 kg per hour to achieve the specified transfer time of 1.25 hours.

	Media Transfer In	Glucose Transfer In	Glucose Fed Batch	Fermentation Broth
Operating Time (h)	1.5	1.25	40.0	1.25
Mass flowrate (kg/batch)	10,000	800	200	11,582
Time-averaged flowrate (kg/batch)	172	13.8	3.4	200
Instantaneous flowrate (kg/h)	6,667	640	5.0	9,266

Figure 6: Fermentation Flowrates

Downstream of a fermentation process, unit operations can be either batch or continuous depending on the process. Cell separation for bioprocessing is accomplished by centrifugation or filtration, usually on a semicontinuous basis interrupted by cleaning steps between fermentation cycles. Further downstream processing (DSP) operations for biofuels and specialty chemicals are often continuous, while food grade products such as proteins often require cleaning of all downstream equipment. In this case, a batch schedule is needed for the entire process, including all DSP steps that require intermittent cleaning. Batch schedules for each unit operation must be determined to estimate instantaneous flowrates for each step in the batch process, yielding a comprehensive MEB in support of the FEL2 cost estimate.

BATCH SIMULATION FOR FEL3

An FEL3-level cost estimate is considered a Class 2 cost estimate with +/-15% accuracy, according to the AACE. To achieve this higher accuracy cost estimate, the process model and resulting MEBs must support a greater level of process flow and equipment detail:

- All flows for each step of the process, including utilities, must be determined so that pumps and piping can be sized.
- Pump and line sizing must take into consideration the layout of the plant so that supply pressures can accommodate distances and elevations between equipment.
- Utility systems equipment must be sized in detail for FEL3, so utility flows supporting each step of the batch operations must be determined.

Many bioprocessing production plants are designed with multiple units of batch equipment, such as multiple fermentation trains. As a result, the batch schedules become complex and difficult to navigate using spreadsheet scheduling. The overall schedule for all equipment in the manufacturing plant needs to be evaluated so that supporting operations like SIP and CIP can be scheduled accordingly, especially for operating steps that share utility resources

Intelligen's SchedulePro software has the capability to take batch schedules developed in SuperPro and combine them into an overall equipment schedule for a complete production campaign. The output is a Gantt chart called an Equipment Occupancy Chart, an example of which is shown in *Figure 7* for a bioprocess employing four bioreactors . The equipment occupancy chart shows equipment utilization as a function of time over the days and weeks of a production campaign. Each distinct color in the chart corresponds to a specific batch. The equipment occupancy chart is useful in identifying bottlenecked equipment (equipment scheduled such that no idle time exists between batches). By debottlenecking the equipment schedule, the rate of production can be increased for the entire plant. For example, an intermediate storage tank can be added if storage capacity is identified as the limiting factor.

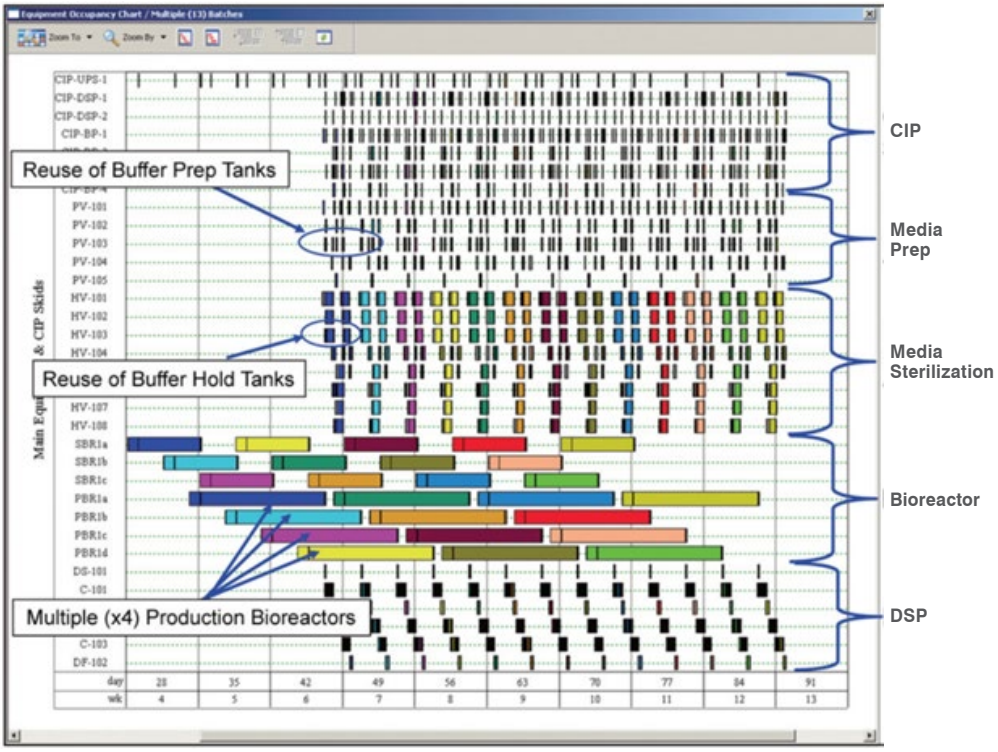

Figure 7: Equipment Occupancy Chart (SchedulePro)

After the batch schedule for an FEL3 design is determined, the MEB can be finalized. Stream tables exported from the model will show data for each stream in each step of the batch operations so that pumps and pipes can be sized. Utility flows and duties can be determined from the batch model, allowing utility equipment to be designed. A steam generation system can be sized for sterilization operations, and chemical cleaning system including mixing tanks, pumps, and automated valves can be designed for intermittent CIP operations. All this information from the batch model is necessary to determine the details needed for all components of a batch process design, thereby providing the client with an accurate FEL3 cost estimate.

CONCLUSION

The MEB is a fundamental process design deliverable required to specify any commercial process. For batch processes, such as fermentation, the overall MEB must be coupled with the batch schedule to define instantaneous conditions that can then be used to specify equipment and utility systems. Batch process simulation tools, such as SuperPro and SchedulePro, are key to developing MEBs and batch schedules used to define, optimize, and debottleneck the process design. The resulting timely and accurate batch processing designs drive key decisions for bioprocess scale-up and commercialization, resulting in estimates that meet capital cost expectations and reduce the risk of future design modifications.

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