1. Introduction

Dynamic manufacturing modeling provides an appealing way to optimize bio/pharmaceutical production. One of the main focal points is programmatically tracking variable changes to study the effects on a process dynamic model. Several different approaches to manufacturing modeling may be used, depending on what effects are targeted. The different approaches can be described as a spectrum across both space of the model and the appropriate time resolution of the model.

A “micro” space/time scale approach is characterized by the requirement for stream physical characteristics and the modeling of unit operation physical phenomena. The single unit operation being studied describes the space boundary and the appropriate time resolution can be minutes to hours. This type of modeling is commonly used in traditional chemical engineering disciplines where the physical phenomena are well understood such as the petroleum or chemical industries. Typical examples of “micro” scale models are simulation of distillation columns or chemical reactors with complex kinetics, mass transfer, and vapor liquid equilibrium. Typical targets of the micro scale approach are financial planning, summary schedule development, and resource planning.

In choosing which model to use, it is important to understand the questions that must be answered and the level of detail available for input to the model. For instance, a micro model is the right choice to optimize the operation of an ultrafiltration step including operating variables such as transmembrane pressure, flux, etc. However, it provides very little data for use in sizing the WFI system for the overall facility. Additionally, the micro model does not generate the economics required to determine the optimum throughput of the plant, nor address whether the additional processing suite provides sufficient return on investment. To answer these questions, the macro scale must be considered.

Using a dynamic model built from different modules facilitates modeling for a wide range of approaches, with particular interest to the macro scale. In the modular approach, generic modules are combined into a manufacturing model utilizing generic code. Additional segments or procedural modules are added to the manufacturing model, as needed, to create the characterization required to focus on and answer the primary questions. Characterizations may range from particular operating philosophies to application of raw material or financial data, etc. With the speed of today’s computer microprocessors and the ease of data sharing between software packages, modular manufacturing modeling with readily available (e.g., Microsoft Office based) software programs is an achievable goal.

2. The Generics

The modular approach is incorporated into all aspects of manufacturing modeling. Process flow modules (or blocks) are added, removed, or modified depending upon the manufacturing process or facility. Programming modules are combined together to form the process blocks. Procedural modules address unique processing activity, both for single programming modules as well as an entire manufacturing model. The procedural modules address unique activity in a simple, reusable method.

A) Process Flow Modules (Blocks)

Every process can be described in a generic block flow manner:

- Product generation blocks contain reaction and fermentation operations.
- Purification blocks contain separation, filtering, drying, and concentration operations.
- Finishing blocks contain filling, packaging, and warehousing operations.
- The resulting “process train” is supported by buffer/media pro-
cessing blocks, further supported by final root utility system blocks (e.g., CIP (clean in place), WFI (water for injection), Waste Handling, etc.).

B) Programming Modules

In a generic manufacturing model, typical data input factors are time, resource and equipment usage. These factors are considered for individual steps, unit operations, and products. Each process block can be described with simple generic modules to organize the data input:

- **Scheduling module** controls what the process makes and when the process makes it.
- **Recipe module** controls how the equipment processes material and what steps are required.
- **Step module** controls what order events occur and any time dependent special processing instructions.
- **Equipment module** controls where the product is produced and what potential flow paths are available for production.
- **Resource module** controls what resources (materials, energy, manpower, etc.) are being used and how much per step.

The main benefit with the generic module structure is that each module can be described in simple table form without being influenced by the other. The dynamic simulation program steps through each module on queue and follows instructions according to the total interaction between all modules.

Additionally, data regarding transfers between pieces of equipment (e.g., process equipment, resource equipment, storage areas, and cleaning equipment) are denoted programmatically so that the dynamics of equipment interaction can be evaluated. The total interaction between all modules is flexible enough to handle interactions between one module and multiple items of a separate module, as well as interactions between one module and only a single item of a separate module. Lastly, a critical aspect of the model is the allowance of easy input and revision to all data input and transfer information.

C) Examples

**Example 1:**

Fermentation/Recovery/Purification

Product A is being queued up by the scheduling module to be made at 6AM according to the steps described in the recipe module. Vessel VE1010 was chosen among a pool of 6 like pieces because others were busy processing batches. The recipe knows to begin filling WFI into the tank, per step requirements, and knows how long to process the batch. It also knows what equipment to transfer to next and will select an appropriate piece when needed. The processing step may take a fixed amount of time based upon the user’s simple table. However, it may take a variable amount of time based upon interactions of modules, such as equipment or resource availability.

The result is a very complicated process evaluation generated by the computer based on simple user inputs. The evaluation can be represented many ways including Gantt chart timelines, which show equipment utilization; resource load trend charts; Plant throughput capacity; and product unit manufacturing costs.

Now that an accurate representation of “process dynamics” can be viewed by the Gantt chart, critical equipment bottlenecks can be identified. All processes have at least one primary equipment bottleneck. Oftentimes a single piece of equipment can restrict the whole process by a factor of 2 or more. Removal of this bottleneck by adding a second like unit can dramatically increase plant performance. Since the computer model is based on modules, it is an easy task to add the second unit, rerun the simulation and observe a new production performance result including increased load on all resources used.

**Figure 1:** Gantt Chart Timeline with Column as the bottleneck equipment - Batches limited to one per 90 hours

**Figure 2:** Gantt Chart Timeline with Second Column added - Batches increased to one per 48 hours

**Example 2:** Buffer/Media

Buffer and media requirements are obtained from resource load trend charts within the computer process evaluation. This information leads to the proper sizing of buffer and media storage and prep tanks and an optimal selection of the quantities of such tanks.

For example, 1,000 liters each of Buffer A are required at 2 PM and 4 PM on Monday and at 4 PM on Tuesday. This information, plus manufacturing requirements regarding how long the buffer can be held before processing, will lead to the selection of the
required vessel size - 3,000 liters if the buffer can be held for over 24 hours, 2,000 liters if it cannot be held for that length of time. Also, 3,500 liters of Buffer B is required at 8 AM on Monday. A selection of 3,500 liters for the vessel volume is intuitive. However, the utilization of a single tank to store Buffer A and Buffer B may not be apparent without resource load trend information from the simulation.

The sizing and selection of buffer and media tanks increases in difficulty with the complexity of the process and the degrees of freedom in the manufacturing operating philosophy. For example, may buffer and media be prepared and stored in a single tank or is there a unique tank for preparation and a second for storage? How long may media or buffer be held before being used by the process? What buffers cannot be stored in the same tank at different times? These complexities can be addressed at any level with an understanding of buffer and media load trend information.

Example 3: Root systems (WFI, CIP)

Root systems such as WFI, CIP, etc, are the most complex to design and the most likely to become bottlenecks for manufacturing facilities. WFI may be used directly in the process as a resource during many steps and may also be used to make buffers and media. In addition, WFI may be used for other root systems such as CIP of process, buffer, and media equipment.

The ability to collect the usage profile information for WFI from all sources within the model is vital to an accurate, efficient design of a WFI system or an evaluation of an existing system. The collection of WFI usage information from many sources leads to an understanding of peak simultaneous demand requirements.

Figure 3: Usage profile for water usage

The collection of WFI usage information also allows the evaluation of acceptable WFI systems. A variety of WFI storage/generation size combinations may be acceptable for a WFI load trend.

A root utility system block can address the effectiveness of WFI storage/generation size combinations. A larger storage tank is able to withstand occasional peaks in WFI demand, thus requiring a smaller generation system. Typically, this is a more economically effective combination. A larger generation system allows the storage tank to be smaller. Typically, this is a better solution where space is limited. A root utility system block can indicate the tank level based upon a specific storage/generation size combination. (See Figure 4). The frequency that the generation system is active is also identified for the storage/generation size combination.

Figure 4: Simulated storage tank level for specific storage tank size/generation rate combination

3. The Dynamics

These examples of a manufacturing model are different from a focused unit operation study or financial study in that the concentration of the model is the dynamics of interaction during manufacturing. In addition to the interaction of multiple unit operations, the manufacturing model accounts for usage of all equipment and storage areas, site preparation of resources, resource receiving from offsite suppliers, personnel requirements, capital and operating costs, etc. What is accountable is dependent on the primary objectives of the model. Oftentimes, it is preferable to begin the model as generic as possible, and add modules to handle additional dynamics as necessary. This approach ensures that the focus of the model is maintained without clouding the original objectives with unnecessary details or data maintenance.

The primary benefit of the dynamic manufacturing model is the ease of evaluating the interactive effects of change. Evaluations can be made from graphical analysis of usage over time. Additionally, modules for performing particular evaluation and summary may be added as necessary.

4. The Modeling of Specifics

The need to model the unique aspects of pharmaceutical manufacturing is a most formidable task. Examples of unique aspects include use of concentrates, recycling schemes, batch pooling and/or splitting, tracking of unit operation details such as reactions or emissions, steady state operations intertwined with batch operations, etc. The modular approach to dynamic modeling allows easy addition of procedures for handling these complexities. Procedural modules can be used to dynamically change operating philosophies, provide additional data requirements, and apply limiting factors to decision making. These procedural modules may be global in nature, affecting how the entire facility is run, or they may be focused on a certain processing step (step procedures).
A) Examples

Example 4:
Fermentation/Recovery/Purification

One method of dynamically changing operating philosophies is tagging a step with a variable that declares that a specific procedure be used when the step is run. This allows the operating philosophy to be considered in parallel to the normal scheduling decisions. In this case, alterations in operating philosophies might be easily handled without programmatic code changes.

As described in Example 1, Product A is being made in vessel VE1010. However, the processing philosophy of the facility is to run 5 days per week. As a result, the step can contain special instructions detailing particular operating philosophies like pausing on Friday at 4PM for a 5-day production week schedule. Each step knows current time of day and status of surrounding equipment for unique decision making.

Similar examples focusing upon activities within a single step are pooling a different number of batches, or moving a batch split to another unit operation. These can be handled by merely assigning, revising, and/or deleting step variables.

Additional data details can be obtained by adding a step procedure which requests additional data from the user (or uses a database) and performs additional calculations with the input data and program generated data. Once again, upon addition of a step procedure to handle the required details, alterations can be easily made by variable changes.

Example 5: Complete Facility

A facility manufactures several products incorporating product generation blocks, purification blocks, finishing blocks, and final root utility system blocks. The facility has a maximum capacity of 50 workers. During modeling, if this number is exceeded, the model could slow down the manufacturing process to maintain the required number of workers below 50. Another option is to have the model move people from less critical areas to more critical processing areas while maintaining 50 workers.

Application of limiting factors to decision making, such as a 50-worker facility, is handled by providing additional procedure(s) requesting user input of limiting factors (or additional functions which can calculate limiting factors) applied during the dynamic modeling of the manufacturing. The application during modeling also requires code to instruct what decisions must be made on reaching the limiting factor. For example, upon reaching 50 busy workers, does the model slow down the process, or shift people from less critical to more critical areas.

Keep in mind that some limiting factors may not be hard rules and might better be dealt with on a trial and error basis, rather than creating a specific procedure for the limitation. An additional procedure for dynamically handling limiting factors should be provided only if the limitation is definite and to be handled frequently.

5. The Simplification

In dynamic manufacturing modeling, time is typically limited, and getting results as quickly as possible is critical. Simplification of varying degrees can help to address and answer the primary objectives of the model quicker. Obviously, a key factor in simplification is the use of additional modules and procedures sparingly. Additionally, less data entry in a generic model results in less data gathering time and less model maintenance time.

For example, consider a study to determine process equipment usage, on a linear basis, and all process equipment is used solely for the process. A model with a single generic step for each unit operation would be sufficient to achieve the objective. In this case, with no resource objectives, no financial objectives, and no step detail objectives etc., very little data input is required to run the model and the primary objective of process equipment usage is met.

At times, reliability of data output can be a price to pay for simplification. The effects of simplification must be considered in determining whether the primary objectives will remain reliable regardless of the simplification. Keep in mind also that there is a price for detail overload, including difficult maintenance of the model, difficult data gathering, and likely slower dynamic performance of the model.