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SIMULATING BIOTECH MANUFACTURING OPERATIONS: ISSUES AND COMPLEXITIES

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ABSTRACT

The Biotech industry is still an emerging application area for simulation techniques. This paper describes the hierarchical discrete event simulation efforts at Bayer Corporation's Berkeley facility that manufactures second-generation recombinant DNA technology based drug, Kogenate-FS®. The facility consists of multiple manufacturing areas housing state-of-the-art biotech processes. The main simulation issues included discretization of continuous activities, building appropriate level of detail in the models and conceptualizing biotech operations for simulation. Complexities arose from spread of manufacturing operations, sharing of common utilities, limited life-span of product and materials in-between stages coupled with limited storage capacities, regulatory constraints, industry-specific quality requirements and varying shift schedules, production capacities and batch sizes across stages. Even though the simulation efforts are not complete, the simulation models developed so far have saved Bayer substantial amount of money and have offered forward visibility for various strategic decisions over the last two years.

1 INTRODUCTION

Biotech manufacturing is an emerging industry. Technological advances like complete decoding of human genome coupled with powerful computers and bio-chips are propelling Biotech manufacturing from lab scale to financially viable operational scale.

Bayer Corporation's Berkeley facility is the global headquarters for Bayer Biotechnology. The facility houses research as well as manufacturing operations. Currently, the manufacturing plants produce second generation recombinant DNA technology based drug (Kogenate-FS®) to treat Hemophilia that is caused by the lack of factor eight protein. As the drug needs to be administered at regular intervals, manufacturing consistency is prime objective for Bayer Berkeley facility.

The manufacturing operations are complex not only from the technology and operations point of view but also due to regulatory constraints that have to be meticulously met and documented in accordance with the agreements with regulatory agencies like FDA (Food and Drug Administration).

Another issue to be kept in mind is that many of the manufacturing processes are indeed at the frontier of research (it is common in Biotechnology to see industry being more active in research than academia). Hence, these processes are inherently unstable in some aspect or another augmenting the problems faced while commercializing them.

2 COMPLEXITIES IN MANUFACTURING OPERATIONS

The manufacturing process is a mix of discrete and continuous processes. The batch sizes vary from stage to stage. Different production stages are physically and temporally separated by intermediate quality control and quality assurance processes. Storage capacities at each stage differ. Product has limited shelf life at each stage of production and product potency is adversely affected by storage. Production capacity differs from stage to stage and so does staffing (in terms of operating shifts and days of the week). As with other manufacturing operations, there are issues of product rejection and process yield.

The concept of rework is significantly different in Biotech manufacturing. The resources blocked by rework are mostly in administrative areas than in manufacturing. Also, there is no re-entrant flow of material.

The cleanliness that needs to be maintained in manufacturing areas is very high. To give an example, an average brain surgeon's room is 'dirty' from Biotech standards. Any compromise to this cleanliness can be fatal for the operations and product. There are elaborate controls to ensure required cleanliness, which create further operational constraints.

3 OBJECTIVES

At Berkeley, Kogenate-FS® was commercialized in 1999 and the manufacturing facilities were combination of new ones and the old ones salvaged from earlier products. This coupled with the complexities stated earlier, made it difficult to gauge the operational capability of Berkeley site for Kogenate-FS® manufacturing. As we were not clear about our existing capability, it was even more difficult to plan for future. Hence, we formulated following objectives for our simulation efforts.

- To understand existing operations and capability
- To identify root causes of operational problems
- To analyze proposed solutions
- To help in forecasting
- To help in strategic decision making process

4 HIERARCHICAL SIMULATION APPROACH

In order to meet our objectives, we evaluated multiple approaches prevalent in the industry like optimization, queueing theory, heuristics, stochastic modeling and simulation. After looking at the complexities presented in section 1, we found that simulation was more appropriate for our needs.

In simulation, we evaluated different paradigms and software and decided on using discrete event simulation and SIGMA® as the software (Schruben 1994). Our requirements from the simulation were as follows:

- At individual process step level, all process details be captured
- At plant level, all processes and operational constraints be captured
- At facility level, all functions and business constraints be captured

These requirements could be met with the following three options:

- Build a large and complex single model encompassing all business processes
- Build a lean but approximate model and sacrifice local details
- Use a hierarchical modeling approach and capture required levels of details

We decided to utilize hierarchical approach for our efforts as it allows developing reasonable model without sacrificing the detailed process characteristics.

The hierarchical modeling approach consists of sub-models and modules. The modules represent a particular process while sub-models are a collection of modules that represent a particular stage of the value chain.

The modules contain the highest level of detail. The sub-models are focussed to represent a particular part of the value chain. The final model utilizes the outputs from sub-models from different levels of the hierarchy.

5 BAYER PROCESS FLOW

In order to describe the hierarchy, it is important to understand the process flow at Bayer Berkeley first. The manufacturing process is driven by fermentation. Fermentation pulls material from the upstream stages and drives the production of downstream processes. Fermentation is a continuos process while others are batch processes. Between any two stages of the value chain, there are Quality Control (QC) and Quality Assurance (QA) steps. QC is responsible for testing material and facilities involved with the stage while QA is responsible for ensuring that all documentation required by regulatory agencies (external and internal) is complete and correct. Figure 1 illustrates the processes at Berkeley facility.

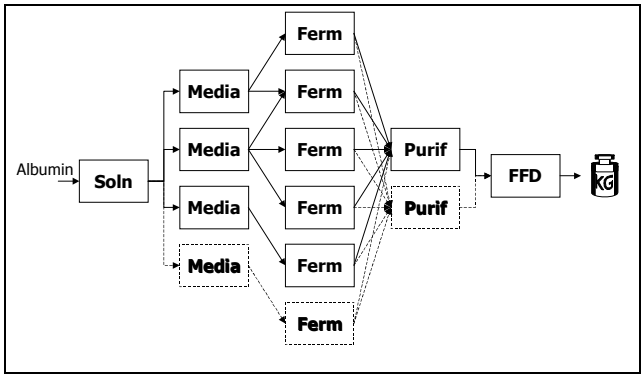

Figure 1: Berkeley Process Flow

Dotted areas above are currently under consideration. The hierarchy evolved from the above process flow and certain operational issues. In discussions with various stakeholders it was felt that certain processes should be modeled in detail while in certain areas lack of data prevented detailed models. Such areas were approximated using black-box stochastic representation. This was achieved using historical data on the time spent by material in that area and the yield observed. This approach proved successful with areas like QA and QC where the administrative nature of the work allows dynamic resource allocation to minimize the impact of resource-capacity constraint. Figure 2 illustrates the hierarchy being used.

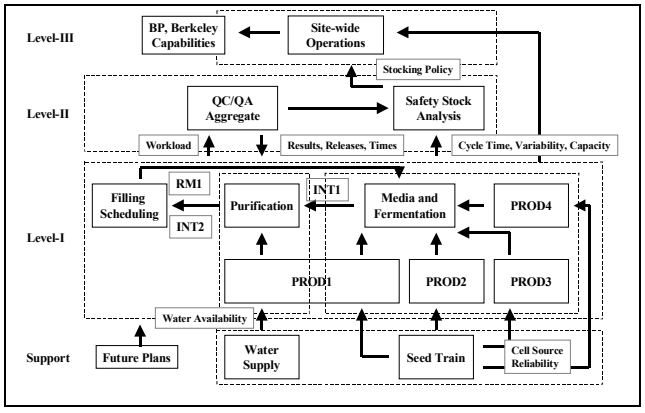

Figure 2: Hierarchical Approach

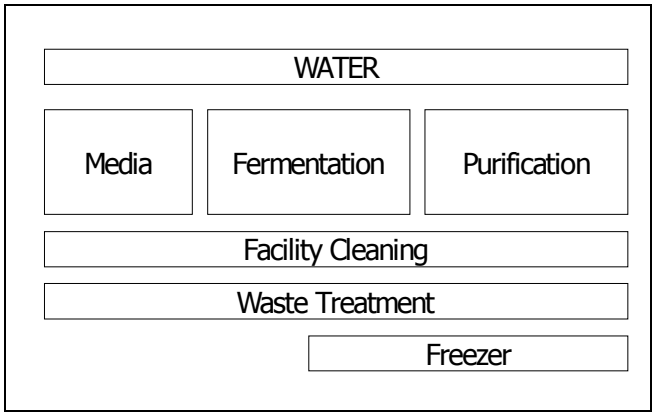

Figure 3: Bayer MBP at Berkeley

The supporting sub-models are the processes where the need for detailed analysis was felt but integrating those processes in other sub-models was thought to develop unnecessarily complicated models.

First level sub-models are the pieces of manufacturing that repeat in different plants in the facility and are stand-alone processes.

Second level sub-models are the processes that require interaction with other areas and hence with other sub-models.

The final model represents a facility-wide operations view that would combine the learning from the various levels of the hierarchy.

The point to be noted is that this hierarchical approach is useful even when it is under development because of the individual sub-models and modules, whereas a large single model would have produced no useable outputs till completion.

6 SAMPLE MODEL

This section describes a few modules and the resulting sub-model from our hierarchical simulation (Saraph and Bamberger 2000a). At Berkeley, we have a multi-purpose biotechnology plant (MBP) that consists of three different manufacturing stages. The whole plant is supported by common utilities like Water (Water For Injection), waste treatment and blast freezers. The plant can operate effectively only when all stages operate in harmony. As each stage is under different functional head, there is little interaction among the stages. Common utilities, equipment and facilities are owned and maintained by engineering and maintenance departments. Figure 3 illustrates the processes in MBP.

In the process shown above, there are various constraints as below.

Within Department Constraints

a. Personnel
b. Equipment
c. Material
d. Processes

Across Department Constraints

a. Shared Personnel
b. Shared Equipment
c. Shared Utilities
d. Regulatory Operating Constraints

In the early simulation efforts, we were not very clear about the kind of linkages that we wanted among different modules and hence, it would be interesting to present how the complexity of our modules reduced after Hierarchical considerations.

The module in question is a process of Purification. The process consists of following steps:

a. Check for the availability preparation space, buffers, raw materials and Water
b. If everything is available, start Purification sequence of multiple columns
c. Process the lot through QC testing and QA release with certain rejection rate and testing and release times
d. Go to (a) and repeat till the end of simulation run

In the Purification step, Water is consumed at over 200 different time points, each for different time length and different flow rates. In our first non-hierarchical module, we developed the logic to check for only 30 main usage points and approximated others. Of course, this compromised the truthfulness of the model. In hierarchical approach, we

were allowed to develop a separate Water supporting model to have a detailed simulation of Water consumption. Hence, in our Purification Module, we just included the stochastic output from Water model in terms of the delay faced due to Water shortage, if any. Figure 4 illustrates the initial event graph while Figure 5 illustrates the event graph after Hierarchical approach.

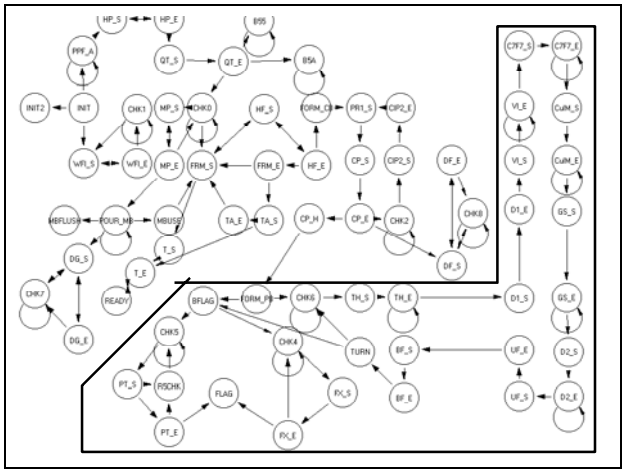

Figure 4: Original Purification Module

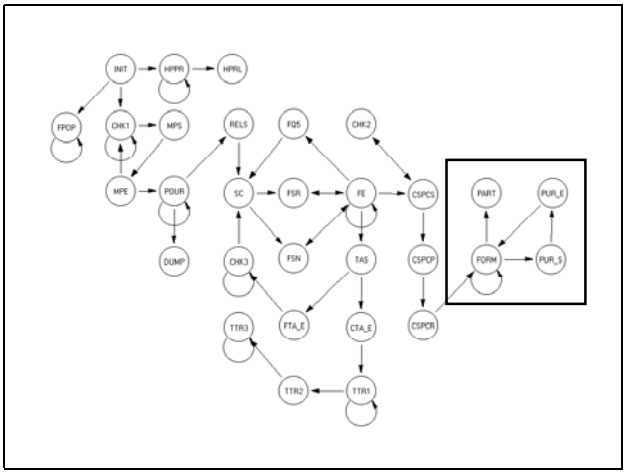

Figure 5: Final Purification Module

In the same way, we were able to resolve the complexity of our other modules as well (the sub-model for MBP was reduced from 71 events, 97 variables to 31 events, 36 variables without sacrificing any information). With the hierarchical approach, our final site-wide model has only 19 events and 22 variables representing the whole Berkeley site processes.

7 CURRENT APPLICATIONS OF SIMULATION MODELS

Individual modules and sub-models have been greatly useful in helping with various strategic and operational decisions for Berkeley site over the last two years and here are a few examples:

Filling-Freeze Drying Capacity and Scheduling Submodel (Saraph et al 2000a)

a. Estimating the throughput of a multi-product, resource-sharing Filling-Freeze Drying facility
b. Strategic capacity projections and impact analysis of capital projects on the throughput of Filling-Freeze Drying facility
c. Identifying significant project-clusters (if done individually, these projects do not increase capacity) for Filling-Freeze Drying facility to improve capacity
d. Supporting budget calculations and projections in short and medium terms

Water Supply-Consumption Supporting Model (Saraph et al 2000b)

a. Establishing root cause for Water shortage
b. Developing Water usage guidelines that minimizes Water shortage (Saraph and Bamberger 2000a)
c. Identifying peak usage demands for Water in terms of flow rate
d. Analyzing impact and utility of capital projects to expand Water capacity
e. Strategic projections on Water availability in terms of future production targets

Media and Fermentation Modules (Saraph and Bamberger 2000b)

a. In each area, identifying the probability of fermentation running out of Media
b. Based on the consumption rate, establishing storage capacity requirements for Media
c. Estimating how much fermentation can be supported with various capacity combinations of Media on site
d. Estimating fermentation outputs based on various stochastic events like campaigns, contamination, titer rate behavior and equipment and personnel issues

The models have also made us think about out processes from a completely new perspective and helped improve our operations (Saraph and Bamberger 2000d).

8 FUTURE USES OF SIMULATION MODELS

Now that we have a clear picture of how our simulation efforts are shaping up, we have planned following applications for the hierarchical simulation models.

a. Site-wide Safety Stock analysis across the supply chain (Saraph and Bamberger 2001)
b. Site throughput analysis
c. Risk analysis for Berkeley operations
d. Capital projects cost-benefit analysis
e. Strategic forecasting on Site capabilities

9 CONCLUSIONS

Given the complex and distinct operations of Biotech manufacturing, simulation is found to be very effective in addressing various operational problems.

Instead of developing one large model or a simpler model, we found the hierarchical approach better that captures the required level of detail without complicating the modeling process.

Hierarchical modeling also offers great flexibility in multiple uses of same simulation models under different conditions.

Hierarchical model development allows the simulation efforts to be useful immediately for the customers rather than having to wait till completion of simulation models.

Discrete event simulation can be effectively used to approximate continuous processes and SIGMA® proved to be a highly versatile software interface for developing and running the simulation models.

Given the nature of Biotech industry and its perceived growth, there is great potential to utilize Simulation as a tool in this industry.

ACKNOWLEDGMENTS

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