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BIOTECH INDUSTRY : SIMULATION AND BEYOND

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ABSTRACT

The Biotech Industry is relatively new to the use of simulation techniques. This paper discusses an application of discrete event simulation in a continuous process Biotech manufacturing facility of Bayer Corporation at Berkeley. The SIGMA® simulation model imitating demand and supply of a critical utility (Water) was used to analyze the Water shortage. The model has been in use for the last year and it has effectively eliminated Water shortages. Based on this analysis, a set of guidelines was designed to ensure better availability of this critical utility. The model initiated a project to reduce the consumption of Water. The model was also used for strategic capacity analysis and to assess the impact of capital projects on future budgetary plans. This whole project was completed in two months and resulted in direct benefits worth $ 1,100,000.

1 INTRODUCTION

This paper presents an example of how simulation is applied in biotech manufacturing (Saraph, Bamberger, Probst 2000b) and how the use of simulation modeling goes beyond basic what-if analysis and estimates of measures of performance.

Bayer Corporation's Berkeley facility is the global headquarters for Bayer Biotechnology. The facility houses research as well as manufacturing operations. Currently, the manufacturing plant produces 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 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).

For most of the manufacturing processes, Water is a critical utility. All equipment and rooms are cleaned using Water, most of the processes use Water for dilution and formulation of process ingredients. Of course Water does not come for free and requires elaborate water treatment. Also, it has limited life. Hence producing, distributing and storing Water to satisfy various demands is a critical success factor for consistent manufacturing.

2 WATER PROBLEM

In the middle of year 2000, the facility started to increase production and Water emerged as a scarce commodity. On one particular day, the production operations had to be halted due to Water unavailability.

As the manufacturing process has stringent constraints on how the product is produced, such a halt created risk for the product. This started a large (spanning 30 days and involving more than 15 personnel from various departments) Quality Assurance analysis of the causes and effects of the halt.

At the same time, it raised the question of how Water demand and supply should be managed in order to ensure consistent production in future.

Differing shift schedules across Water consumers, variability in usage times and quantities, uncertainties in the Water supply and future plans to change production output as well as Water supply capacities created a need for a detailed and reliable analysis of Water demand and supply.

3 OBJECTIVES

- To understand the reasons behind Water shortages observed
- For different production load scenarios,
  - To estimate the peak Water demands
  - To analyze the impact of different capital projects on Water availability

4 APPROACH

While analyzing different options to develop a solution for Water problem, it was realized that the non-linear, stochastic and discrete nature of decision variables posed a significant difficulty in developing any exact solutions. Hence, simulation using SIGMA® was chosen as the tool (Schruben 1994).

SIGMA® Simulation also meshed with our other process optimization efforts where we are making extensive use of simulation (Saraph, Bamberger 2000a).

We followed the standard approach for simulation studies of process mapping, data organization, logic development, model building, validation, experiments, iterative changes, results and analysis.

5 SCOPE

The project covered Water manufacturing facility, two Water consuming production plants and within each plant five Water consuming departments. Total number of Water consumption points modeled across the two plants were around 600.

The model took into account the differing shift schedules of various departments, variability in Water consumption times, failures of equipment in production plants and Water manufacturing facility. It also considered the facility constraints (e.g.- Water supply loop has to be sanitized twice a week, Wednesday and Sunday swing shift from 7:00 PM to 11:00 PM, hence Water usage is blocked from 7:00-11:00 while Water is drawn from supply tanks for flushing the loop from 9:00-11:00 PM).

The model also accounted for problems with product or product supporting materials being prepared using Water. Such problems cause either delay at other consumption points or create excess Water demand.

6 MODELING LOGIC

Due to the continuous nature of the processes, Biotech Manufacturing has reasonably predictable weekly production schedules. Also, as the model was expected to analyze different production load scenarios, we decided to have production schedule as the model input.

The model input created a Water demand schedule. We developed an independent Water supply logic to reflect the reality. Then, we created logic for Water demand and supply to interact with each other as illustrated in Figure 1.

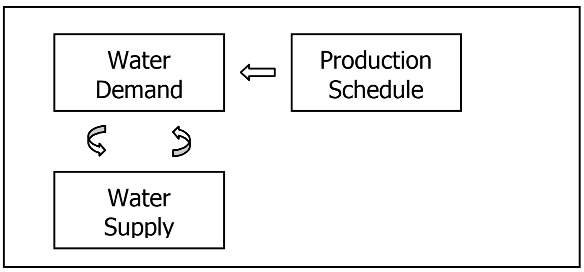

Figure 1: The Water Modeling Logic

This logic captured the real life interaction between Production personnel (Water consumers) and Engineering (Water suppliers).

6.1 Conversion from Continuous to Discrete Process

As Water supply and consumption are continuous processes, our first task was to truthfully map the continuous nature using discrete event paradigm.

Water manufacturing facility has a certain production rate capacity of, say, X liters per minute. We proposed that the continuous supply should be looked at as a collection of discrete packets. As the production rate is constant (for all practical purposes), if we define each discrete packet as unit output per time unit, then we have a discrete batch manufacturing process .

Such discrete process manufactures one batch of X liters in 1 minute with zero changeover time as illustrated in Figure 2.

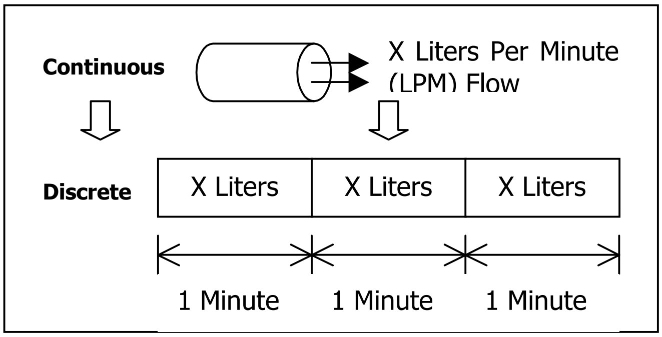

Figure 2: Discrete Approximation

6.2 Water Suppliers and Consumers Interaction

Such communication used to be on a weekly basis for planning purposes and by exception for day-to-day operations. In order to avoid damage to equipment by Water unavailability, there are certain constraints hardwired in the centralized computer control system (DCS).

Due to the existing lack of clear communication, future visibility was quite poor for Water planning. Hence, the model captured this lack of future visibility by shutting off Water supply if Water tank level fell below the threshold value.

Water consumers then keep on checking with suppliers as to when Water would be available, which was modeled as Water level checks by different consumers at regular time intervals.

Such unavailability has serious implications for production and if Water unavailability exceeds certain time limits, the whole process step has to be repeated. Which was modeled by triggering the repeat based on Water unavailability time. The only aspect that we could not model was the verbal debates between suppliers and consumers!

7 BUILDING THE SIGMA® SIMULATION MODEL

Due to the short time-span of this project (two months), planning was very important and hence while building the model, we followed a modular approach. During our data organization and analysis phase, we captured various rules and logic that governed Water supply and consumption.

We developed common consumption logic and the supply logic based on data. After debugging this logic, we modified the common consumption logic to fit different consumption patterns from different production areas.

While combining our consumption and supply logic, we superimposed the ‘interaction logic’ either at supply stage (e.g.- no supply if the tank level falls below 10,000-liters) or at consumption stage (e.g. - can not start consumption unless available Water is more than or equal to 18,700-liters). Data organization and model building took around two weeks.

8 VALIDATION

For the model results to be accepted by line management, it was crucial to show that the model was reflecting the reality. As the line management was not very familiar with Simulation, the mathematical or statistical measures of validation were not of much use. Hence, we started to look for some measure of performance that could be easily understood by the line management.

One such measure was the Water tank level over a week. Water tank level is monitored by the centralized computer system at the interval of five minutes. Hence, the line management is very familiar with the graph of Water tank level over a week.

We decided to simulate one particular production week (21st to 28th May 2000) for such validation. If the model could replicate the Water tank level for this week, it would imply that it is capturing Water supply and consumption realistically. One-week time span was chosen as the whole consumption pattern repeats every week.

As can be seen in Figure 3, the model replicated real life behavior truthfully. Average difference between model values and actual values was found to be 9%. More importantly, the line management developed faith in the model as they could see the model doing something that they could relate to.

The differences in peak values and temporal lag between model and actual values were attributed to the variability in daily operations that could not be verified for the validation week. For example – when an operator was supposed to use 100-L of Water, he might have used 90 or 120-L, also a particular operation might have been off schedule by certain time. Model validation took one week.

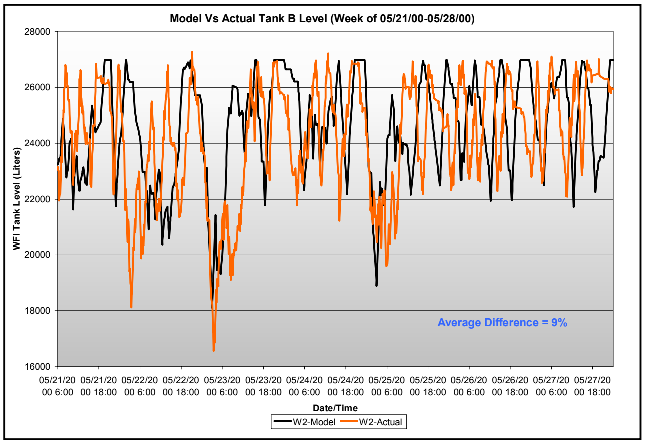

Figure 3: Validation of the Model

9 REASON FOR WATER SHORTAGE

After validating the model, we ran the base case scenario to analyze the reason for Water shortage observed. We found that Water shortage occurs whenever the Water consumption schedules of two main consumer departments (Consumer-A and Consumer-B) match closely in time.

As can be seen from figures 4, 5 and 6, the Water tank level drops suddenly when these two consumers’ Water consumption patterns overlap each other. This analysis was generally known in the past, but the SIGMA® model clarified it in numbers and validated it.

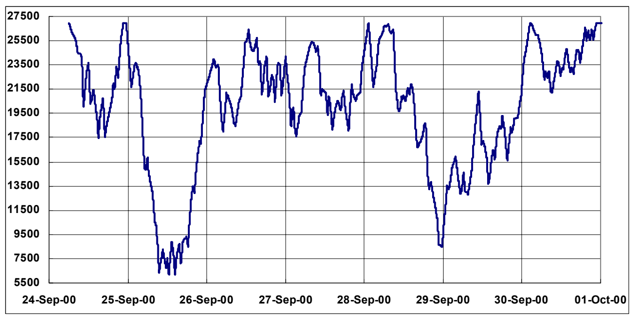

Figure 4: Water Tank Level in Liters Over One Week

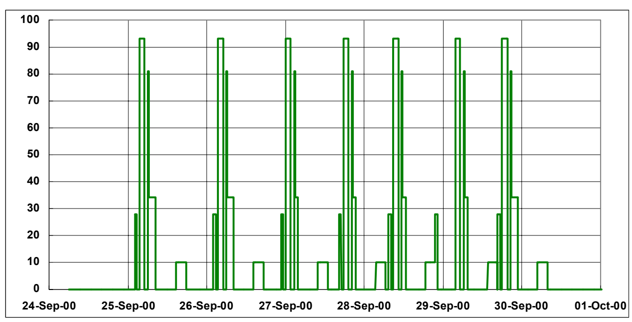

Figure 5: Water Draw in LPM from Consumer-A

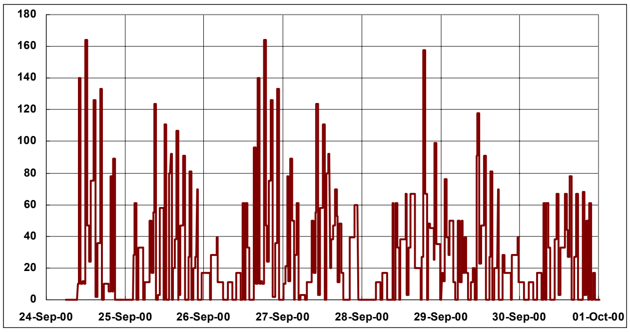

Figure 6: Water Draw in LPM from Consumer-B

10 EXPERIMENTS

After analyzing the reason for Water shortage, we started to build experiments to answer the remaining questions raised in the objectives section. Our scenarios were as follows:

Table 1: SIGMA® Simulation Scenarios

Production Load ➔	Base	2001-A	2001-B	Maximum
No Projects	✓	✓	✓	✓
Project A	✓	✓	✓	✓
Project B	✓	✓	✓	✓

Each of the projects was a capital project proposed to improve Water availability in future. Project A was a temporary solution proposed, while Project B was a large capital project spanning two years.

The production load scenarios depicted different production levels proposed to match Bayer's future plans. Maximum production load scenario depicted the maximum physical capacity of all the equipment in our two production plants.

The experiment output was designed to offer insights into each scenario and thus help the management make decisions. Hence, we developed the following measures of performance.

- Number of times operations wait for Water per department per week
- Average wait for Water per operation per department
- Number of times Water tank level falls below the threshold level per week
- Minimum Water tank level observed over simulation run span

Each experiment consisted of 40 replications of a terminating simulation experiment with same starting conditions and different random number seeds. Each measure of performance was stated as a mean with 95 and 99 percentile level of confidence.

The experiments took around one week and results analysis took another week. The results indicated that to meet 2001 production budget, we had to execute Project A till Project B was completed. It also indicated that with Project B completed, the Water supply could support the maximum production load as well.

11 BEYOND SIMULATION : WATER USAGE GUIDELINES DEVELOPMENT

This was the starting point for our efforts beyond the normal 'what-if' analysis. As project A was going to cost us in terms of resources, time and money, we decided to find out if it was possible to abandon project A.

When we looked at the SIGMA® model results, we realized that the Water shortage was being caused not due to lack of capacity of the Water supplying facility, but rather due to the wrong timing of Water consumption (refer to Figure 4).

Hence, we ran a second set of experiments where we tried to find out how much time would be required between any two large Water consuming steps so that

- Production schedule is met for the week without significant delays, and
- Water tank level does not fall below the threshold level causing Water supply to stop

Through our simulation experiments, we found that if major Water consuming steps could be separated by four hours, Water supply had enough time to rebuild Water tank level. Also, if the largest Water consumer checked before starting that Water tank level was above 18,700-L, then that operation would not have to halt in between.

Based on these observations, we built Water usage guidelines for Water Suppliers, Water Consumers and Plant management.

As these observations were additional constraints to already complicated production operations, we not only had to sell these guidelines to line management but also ensure that the guidelines were simple to follow, did not require any change to the existing systems and were sustainable in daily manufacturing operations.

Through multiple meetings and negotiations with stakeholders, we institutionalized these guidelines and they have been in operation now for more than one year.

The guidelines along with our analysis have been effective, as there have been no Water shortage incidents for the last year. Please refer to Appendix-A for these guidelines.

12 BEYOND SIMULATION: PROJECT TO SAVE WATER

Water being a costly commodity, this project also raised the question as to why do we need so much Water in the first place. Subsequently, we asked the question, where could we save Water?

The question led us to an opportunity to not only save Water but also to eliminate a particularly lengthy process step (60 man-hours per week) from one production area.

This elimination saved Water, saved production time, improved ease of operation and made the process more flexible. The total estimated benefit from this project was $ 500,000 per year (Saraph et al 2000d).

13 CONCLUSIONS

1. Continuous manufacturing processes can be truthfully simulated using discrete event simulation
2. Communicating the simulation results in a language familiar to your customers is crucial for a successful simulation project
3. Use of simulation is not limited to classical 'what-if' analysis, but it can be successfully extended to gain better insights into the system under simulation and initiate improvements beyond simulation
4. SIGMA® Simulation model has been established as a strategic decision support tool for future Water related issues
5. The simulation project saved Bayer Berkeley capital project worth $100,000, prevented lost production worth $500,000 per year and initiated another project with realizable benefit of $500,000 per year
6. The simulation project also helped to improve manufacturing operations, led to stable production schedules and offered better predictability for operations planning.

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APPENDIX A: WATER USAGE GUIDELINES (SARAPH ET AL 2000C)

Managerial Guidelines

- Fix production schedule at least for the next 2 weeks
- Arrange weekly Water planning meeting to discuss and generate next week's Water consumption schedule for major activities (Consumer-A and Consumer-B) separated by ± 4 hours. This meeting shall roll up into Friday's meeting (Engineering-Production-Maintenance co-ordination). Last week's Water usage and conflicts will be part of the agenda and the discussion will be used to refine the guidelines
- Communicate large Water draws as early as possible (at least 4 hours in advance)
- Adjust the weekly schedule in order to account for the variability (like Consumer-A rejection, bin availability and buffer rejection) as frequently as possible (at least once every shift). Such adjustments shall happen once every day during the Engineering-Area Supervisor meeting of 08:00 AM.
- For every production shift, there needs to be one person responsible for monitoring Water tank level. This responsibility can be rotated among Consumer-A (Consumer-A), Consumer-B (Consumer-B) and Engineering.

Water Supplier Guidelines

- Keep both stills (Water production outlets) running at all times. Notify production areas of planned shutdowns and maintenance at least 1 week in advance. Planned Maintenance schedule is known for 1 year in advance, but random failures would require co-ordination between Water Supplier and consumers
- Ask Water consumers to postpone fresh Water usage, if tank level drops below 10,000-L, but allow them to complete the draws that are in progress. Convey the consumers when Water tank level builds back to 10,000-L
- Ensure that the tank level is 8,700-L above shutoff level, when Consumer-A asks for Water for formulation, if not, ask Consumer-A to wait till this level is reached.

Consumer-A Guidelines

- Consult with Water Supplier before (at least four hours in advance) commencing the large formulation draw to ensure adequate Water supply

- Forecast the time-points of production lots a week in advance within ± 4 hours. Note that this will be a forecast, not a schedule! Such forecast can be provided for a complete week.

Consumer-B Guidelines

- Avoid drawing water for more than two operations at the same time i.e. try to maintain total draw rate below 100 LPM. This should not be a problem as usually water is drawn for not more than two operations at a time
- Consult Consumer-A and Water Supplier before (at least two hours in advance, preferably four hours) commencing large buffers in order to avoid large parallel draws on Water tank
- Try to space out Water draws in a shift (at least by one hour, preferably by two hours). Though possible under normal operating conditions, there might be some instances of back to back Water consumption. In such case, Consumer-B should notify Water Supplier at the earliest

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