

Use of Simulation in the Design of a Pharmaceutical Process

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Abstract:

Building a dedicated facility for manufacturing a drug is a major decision for a pharmaceutical company. Due to its inherent flexibility, the batch mode of operation, used in almost all pharmaceutical processes, allows you to start with modest design capacities, thereby reducing the initial capital investment. However, a design is not complete until you evolve a clear strategy for increasing the process throughput in order to satisfy future demand. In addition to support system constraints, a pharmaceutical process will have operational and often material stability constraints. The operational constraints imposed by the FDA on drug manufacturing complicate the development of such a strategy. The operating procedures and rules for all processing steps are a part of the drug approval step and must be strictly adhered to. Thus, the original plant design as well as future additions must conform to these procedures. Therefore, it is not adequate to merely identify the stages where new equipment will be added to increase the process throughput. One must ensure that the expected increases in the throughput will be realized when the changes are implemented. Simulation is the ideal tool for studying these types of problems. The BATCHES simulator was used in evaluating various design alternatives. The simulator accurately modeled the complex operating procedures and rules associated with the manufacture of the drug. Simulation was used to study the impact of support systems, process yield variability, and operational procedures on process performance and robustness. In addition, the impact on support systems and operations imposed by future capacity expansion was analyzed. Based on the simulation results, the following type of design decisions were made: equipment sizing, number and sizing of support systems, operational parameters along with factory loss risk profiles.

Introduction:

Most of the bulk pharmaceutical processes operate in a batch mode. The inherent flexibility offered by this mode of operation allows you to start with a modest design capacity, thereby reducing the initial investment. However, a design is not complete until you evolve a clear strategy for increasing the process throughput in order to satisfy future demand. For example, initially you may build a facility with one train of key equipment and later on add another train when the demand reaches a minimum threshold. In a good design, provisions are made for accommodating future revamps in the most economical way.

A typical pharmaceutical process consists of mainstream processing steps as well as steps associated with support systems such as Cleaning in place (CIP), Sterilization in place (SIP), Water for injection (WFI), raw material preparation, reworking of material, analysis of material in laboratories, etc. One of the unique features of bulk pharmaceutical manufacturing is that the detailed recipe specifications must be validated and authorized by the Food and Drug Administration (FDA) on an existing manufacturing facility before the product can be sold to the end user. Of course, once authorized, the recipe

specifications must be strictly followed. This has a significant impact on evaluating design alternatives, because the time and expense required for FDA approval must be taken into consideration for each alternative.

The manufacturer has considerable latitude in developing the recipe specifications. Thus, development of recipe specifications becomes a part of the entire process design. For example, suppose in the beginning you want two reactor trains in the process, each train fed by two preparation tanks. When you add another reactor train, you may need only one additional preparation tank and change the connectivity of the others so that they can be shared more effectively. Therefore, if you anticipate making such a process change, then the recipe specification may be developed accordingly prior to submission to FDA. This could avoid some of the costly delays when process modifications are made.

In addition to support system constraints, a pharmaceutical process may have material stability or other operational constraints. For example, certain analysis steps, which are performed in analytical laboratories, have a minimum turnaround time. Also, due to stability limitation and increased potential for contamination, material cannot wait in a particular stage for more than a specified maximum time. These types of constraints become critical as the competition for resources increases during plant expansion phases.

A couple of years ago, Eli Lilly made a decision to build a brand new, dedicated, biosynthetic bulk drug manufacturing facility in Indianapolis, IN. A detailed BATCHES simulation model of the proposed facility was used to validate and quantify some of the design decision. The decisions made by the Lilly design/development team and the engineering contractor were often based on experience. Eli Lilly's simulation team worked very closely with these teams and optimized several of the process cells. Additionally, the impact of future changes was simulated to make adjustments to the initial operational specifications. This paper describes some of the key decisions that were assisted based on simulation. First, the underlying process is described. This is followed by a summary of various simulation runs and the impact on the design.

Process Description:

The recipe for the manufacture of the biosynthetic bulk drug consists of numerous processing steps. The schematic diagram of the key steps in the recipe is given in Figure 1.

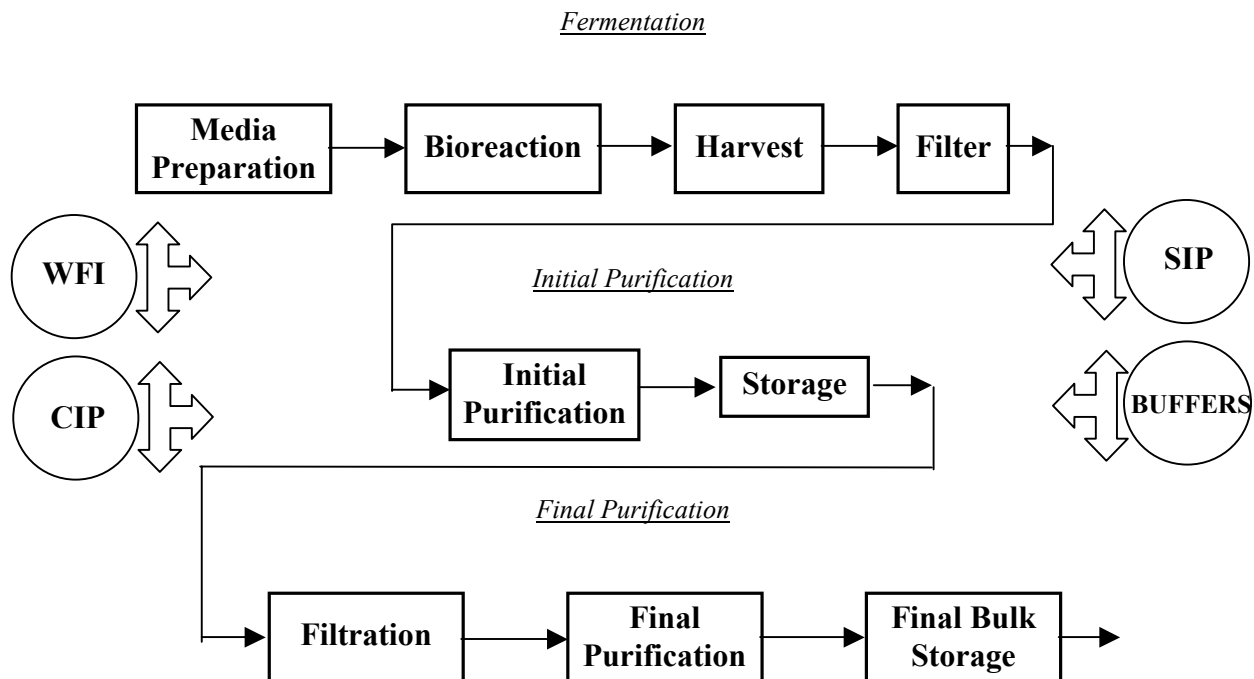


Figure 1: Schematic diagram of the biosynthetic process.

Bioreaction: The bioreaction stage consists of operations that produce the active compound.

The Media Preparation operations consist of preparing the material that is charged to the bioreactors and the nutrients that are fed continuously during the reaction.

The bioreaction takes place over several days. The cells are harvested continuously and stored in a harvest storage tank. Approximately once every day the contents of the harvest tank are sent downstream for harvest and filtration. Each bioreactor has a dedicated set of equipment to process the material through cold storage in the Initial Purification stage. Thus each bioreactor has dedicated harvest tanks, filters, columns and so on. The media preparation operations use a common set of shared equipment for all reactor trains. The harvest tanks after the bioreactors alternate between collecting material from the reactor with subsequent feeding to the harvest area.

Initial Purification: This stage consists of operations associated with the first purification.

The operations consist of preparing batches of material containing the appropriate amounts of active compound and preparing elutriants for product recovery. The batches of active compound are charged to the chromatographic columns. The active compound is recovered by feeding a suitable elutriant to the columns. The active compound is first collected in the mainstream collection tanks, and then kept in storage awaiting further processing. The streams from each train converge in the final purification operations.

Final Purification: The operations in this stage perform the final purification of the product.

The material from storage is first loaded into a tank associated with separation. After a series of intermediate steps the final purification is done using a chromatographic column. The finished product is stored in final bulk storage.

WFI System: The WFI system consists of a still that produces very high purity water. The water is stored in an intermediate storage tank and is used throughout the process for media and buffer makeup, flushes, process steps, and CIP systems.

CIP System: After each batch, each piece of equipment goes through a CIP cycle. The CIP operations are not shown in the schematic recipe for the purpose of clarity. There are several CIP systems in this process, each is assigned to a specific group of equipment. Only one piece of equipment per CIP system can be cleaned in place at a time.

SIP System: Certain steps throughout the process require sterilization in place. Several simultaneous users can be SIP'ed at once.

Preliminary Design:

The business unit provided the initial design throughput for the process based on the demand forecasts. Subsequently, the Lilly design team and the engineering contractor completed the preliminary design of the facility.

The bioreaction, which produces the active ingredient, is clearly the most critical stage in the process. The decision about the number of bioreactor trains and scaleup of those trains was an important decision in the facility design. The number of bioreactor trains was determined based on the scaleup comfort of the design and development personnel and the required design throughput.

The preliminary design of the facility was based on the number of reactor trains. Deterministic information was used about the cycle times and yields to compute the number of pieces of equipment at each stage in the mainstream processing. The initial design of support systems was based on experience.

Simulation Runs:

Eli Lilly's simulation team constructed a detailed BATCHES simulation model of the entire production facility resulting from the preliminary design done by the Lilly design/development team and the engineering contractor. All three teams worked in concert to evaluate the impact of various alternatives. During this study hundreds of simulation runs were made. A summary of some of the important decisions that were impacted by simulation is given in this section.

The process is highly integrated because of the shared resources and support systems. Therefore, even when the focus of a specific set of simulation runs was a particular process cell, the entire process model was used in each run to make sure the impact due to the coupling is not ignored. The time span in all simulation runs was one year.

Loading of Final Purification Stage:

One of the most important design decisions is the loading on the Final Purification stage. In essence, this stage determines the average process throughput. The loading is defined as the minimum and maximum limit on the mass of active compound charged to this stage. After Initial Purification stage, the active compound is stored in separate lots in cold storage. The amount of active compound in each lot is different, because it is determined by the time at which the associated material is harvested. The data on daily yield was provided by the pilot plant studies. Also, material in cold storage is time stamped. If a lot stays in cold storage beyond a specified maximum time, it must be discarded.

The simulation model was used to evaluate the impact of mixing material from different bioreactor trains for the final purification. Having the ability to combine intermediate material from more than one bioreactor lot into a final purification lot minimizes the chances of having to discard the intermediate product due to expiration. However, mixing intermediate material from multiple bioreactor lots also increases the potential product loss if we later found out that one of the intermediate streams did not meet its quality requirements.

The sizing of the final purification stage was determined based on several simulation runs. The following parameters were changed during simulation: variability in the yields at each operation in this stage, minimum and maximum limits on the process loading, and the frequency of operating this stage. The main performance measure monitored during the runs was the amount of finished product produced within a certain composition range. Based on the statistical analysis, the final column size and the size of the final storage vessel were determined.

The design satisfied the criterion that for the selected mixing rule, the risk of violating a process parameter is extremely low. These design parameters and the mixing rule were submitted to the FDA.

Another simulation run showed that the mixing rule and loading would be adequate if an additional bioreactor is added to the process. This simulation also clearly indicated the effect of this process change on the downstream purification process steps.

WFI System Design:

The main design decisions in the WFI system design are the still throughput and the size of the intermediate storage tank that stores the purified water. The users of WFI constitute the load on this system. In addition to the new process, the WFI system was designed to supply other users also that run in parallel to the current process. Although the parallel users were not modeled in detail, their loads were represented as constant rates with specific patterns of use for specified durations.

Since the WFI system was integrated into the overall process model, the load on the system accurately portrayed the reality. The still throughput and tank size were determined by trial and error. Several simulation runs were made by changing the still throughput and tank size, and observing the average, minimum and maximum tank levels. A snapshot of the filled volume fraction profile in the WFI storage tank is shown in Figure 2 and a snapshot of WFI draw rate profile, the load on the storage tank, is shown Figure 3. The combination for which the tank level did not drop below a safe minimum was chosen as the final design.

A simulation run showed that the proposed still throughput would be adequate for additional bioreactors also.

SIP System Design:

The design contractors for the project provided the steam usage profile (steam flowrate in rate vs. time) for a typical SIP cycle for the various pieces of equipment that require SIP. The continuous profiles were discretized in 5 segments for use in the simulation model. There was no constraint on the number of simultaneous SIP users. Based on the plantwide steam usage profile from a simulation run, the peak demand, and the average demand and the maximum number of simultaneous steam users were determined. Examples of plantwide steam usage profile and profile of number of simultaneous steam users are given in Figure 4 and Figure 5, respectively. These values helped establish the adequacy of the proposed steam generation system for two and additional bioreactor trains. The Automation group in designing the batch control logic used the maximum number of simultaneous users.

Buffer and Media Makeup:

The process consumes 11 different buffers throughout the Purification stages. Each buffer has a dedicated hold tank. The buffers are made in makeup tanks. The design team needed to determine the number of buffer makeup tanks required for the process. For the proposed number of buffer tanks the utilization was studied based on different makeup times and operational philosophies.

For certain buffers, fresh batches are made every time they are required, while for others a certain minimum and maximum levels are maintained in the hold tanks, that is, once the level in the hold tank drops below the minimum, a make up is scheduled to top off the hold tank. As the make up trigger level is lowered, fewer make ups are required but the risk of

running out of material increases. The simulation runs allowed us to determine the number of make up tanks that would be required for an average minimum trigger level of 20% full for hold tanks. However, quality restrictions required the final design to remove the keep full operating philosophy. Thus, simulation was used to analyze the total fresh batch make up philosophy.

The media makeup tanks feed the hold tanks, which in turn feed the bioreactors. Due to the contamination considerations, a set of media hold tanks is dedicated to each bioreactor. After a media makeup tank transfers material into the hold tank, a sterility test is performed before it can be fed to the bioreactor. If the sterility test is negative, the material in the hold tank is thrown away, requiring additional media makeup. The duration of the sterility test depends on its type. Of course, the more rigorous a sterility test, the longer its duration. A sterile media makeup batch must become available within a specific time window. Otherwise, the bioreactors get starved, an extremely undesirable effect. Several simulation runs were made by changing the number of media makeup tanks and makeup times, media hold tanks, connectivity constraints and sterility test times. Restricting the number of hold tanks that feed a bioreactor reduces the risk of cross contamination, but requires enhanced makeup capability and reduced sterile test times.

The simulations were used in determining the maximum sterile test time, if the hold tanks were dedicated to bioreactors and certain turn around on the hold tanks was to be achieved. The analytical laboratory deemed this maximum limit on sterile test time risky and unachievable. As a result, a flexible hold tank configuration was used in the design and a suitable batch automation logic was developed.

CIP System Design:

The main design decisions for CIP systems are the number and the capacity of each system to be included in the process, and the assignment of specific pieces of equipment to each system. Typically, the CIP durations are identical for a majority of pieces of equipment. The engineering contractor proposed the configuration and capacity of all CIP systems based on past experience. The simulation model was used to verify the adequacy of the systems at different cleaning times, media and buffer makeup schemes, and process throughput.

The CIP utilization profile shows periods of very high utilization and periods where the utilization is low to moderate, see Figure 6. Also, the effect of adding an additional bioreactor train was studied. The simulation showed that three CIP systems would be sufficient if we added an additional bioreactor train using average CIP time of approximately 1.0 hr.

Conclusions

A very detailed BATCHES simulation model of Eli Lilly's brand new bulk pharmaceutical manufacturing facility was constructed based on the preliminary design proposed by the design team and an engineering contractor. The model was comprehensive in scope that included mainstream equipment as well as all support systems. As a result, the model provided very accurate and reliable quantitative information about the impact of various design alternatives on the entire process. In the entire study, more than 100 simulation runs were made to evaluate design changes. Many design and capacity decisions were either based on, or were validated using the model.

The model also provided data to the automation group for programming the batch controllers. It will continue to provide value when it is adapted for making day-to-day production scheduling decisions after the process is fully functional. Aside from reducing the capital investment by optimizing the design, the model validated the operating conditions that were submitted for FDA approval, and identified critical areas from the standpoint of future modifications. The design and operating procedures were suitably modified so that future process revamps will be least disruptive.

References

1. BATCHES Users' Manual, Batch Process Technologies, Inc., 2001.

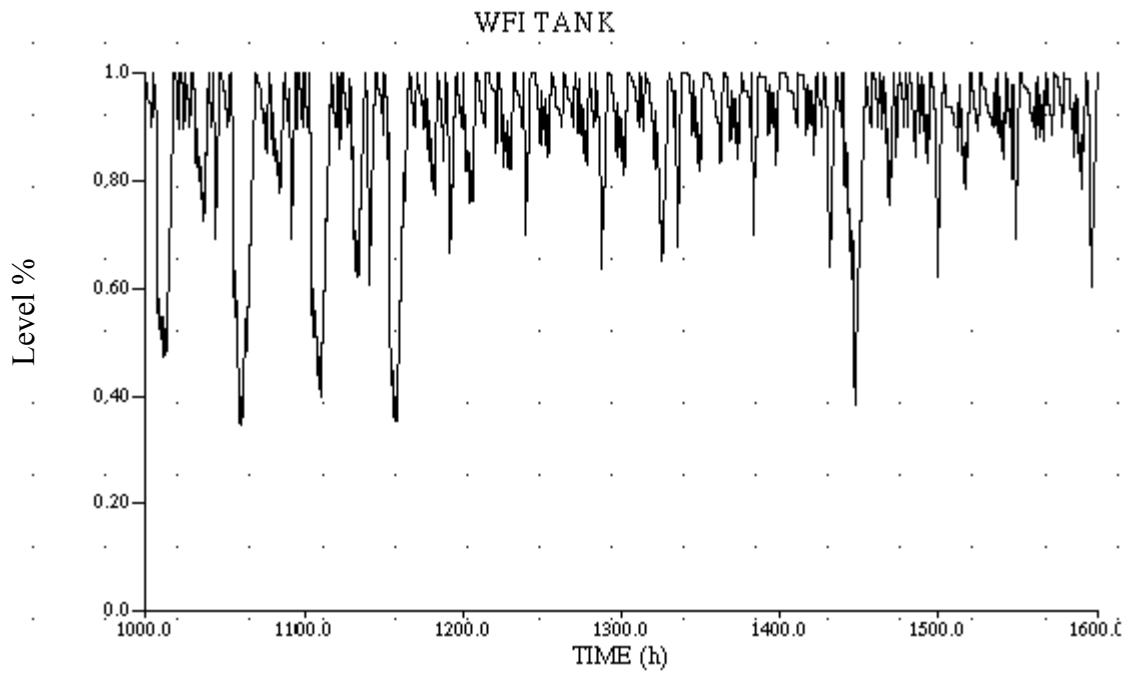


Figure 2: A snapshot the WFI storage tank level.

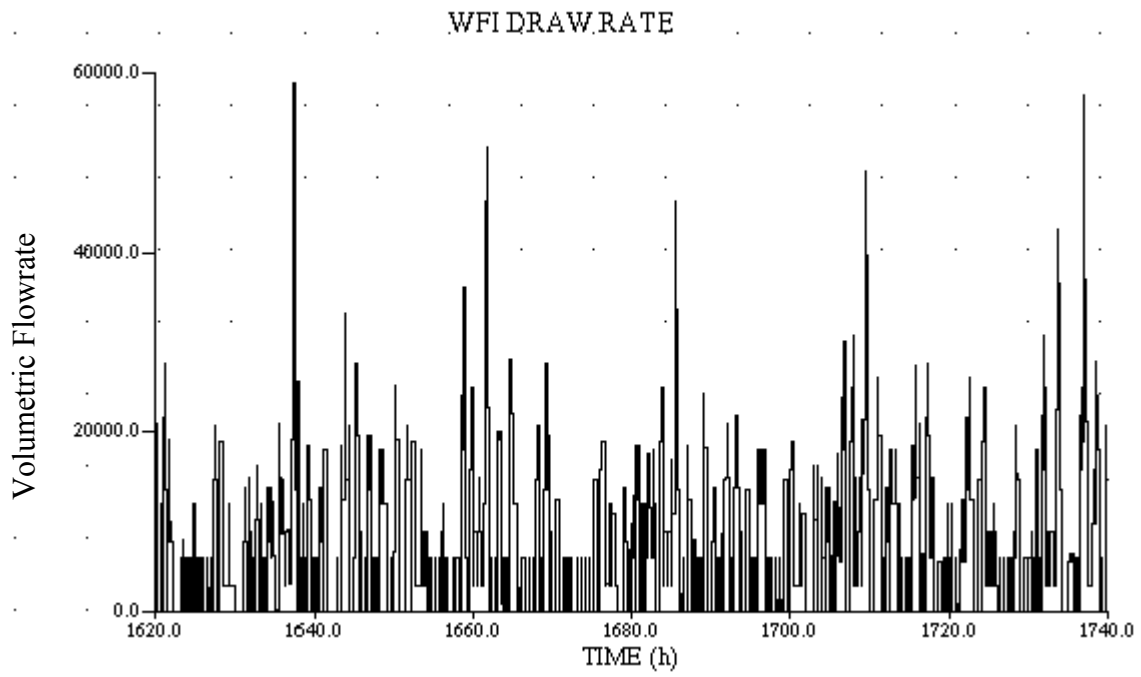


Figure 3: A snapshot of WFI draw rate profile.

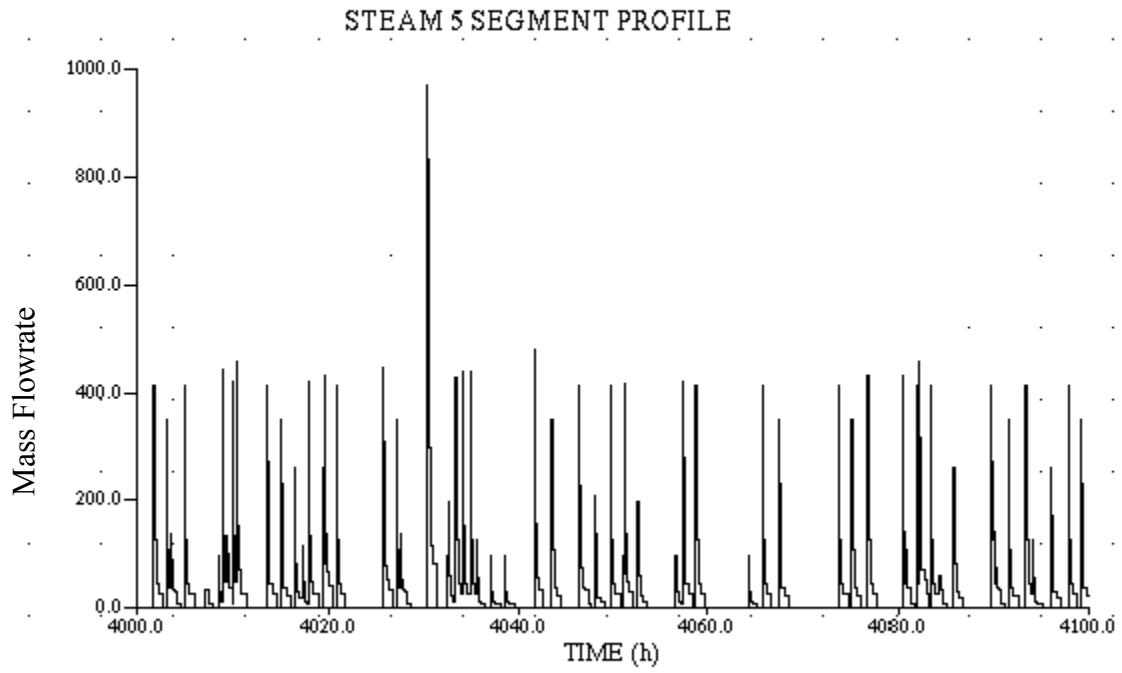


Figure 4: A snapshot of steam usage profile.

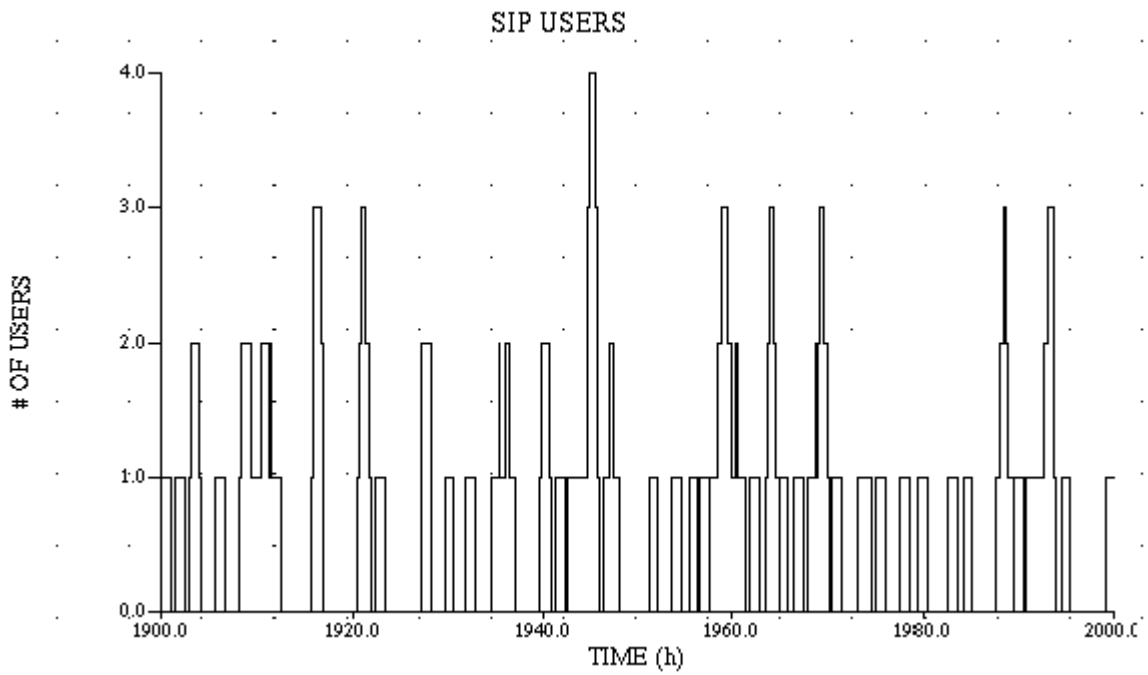


Figure 5: Profile of simultaneous steam users.

CELL CULTURE CIP UTILIZATION

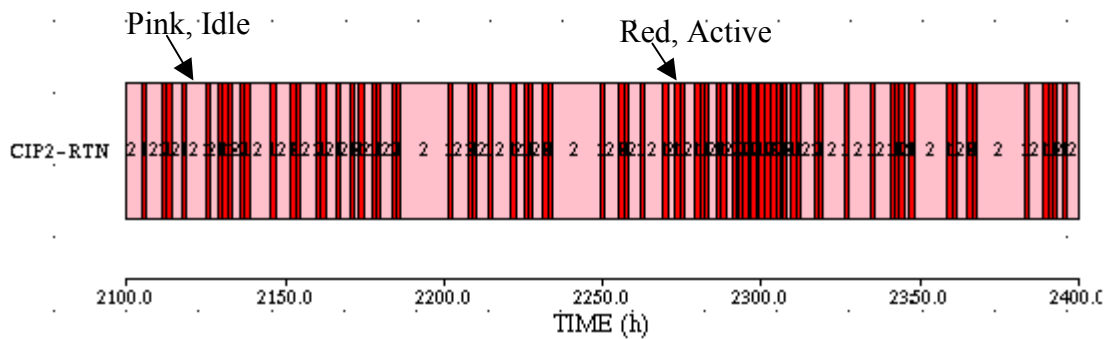


Figure 6: Gantt chart of CIP utilization.