PRACTICAL APPLICATION OF SIMULATION AND CAMPAIGN SCHEDULING OF THE MANUFACTURING PROCESS BASED ON MONOCLONAL ANTIBODY

By

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ABSTRACT OF THE THESIS

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Monoclonal antibodies are the fastest growing segment of pharmaceutical molecules. Currently, they are used as diagnostics, therapeutics for various medical uses as well as in protein purification. They are among the costliest drugs available in the market. In recent years, due to the competitive pharmaceutical market and incentives for antibody development, biotech industries are investing in novel and advanced technologies to increase the productivity as well as the efficiency of the process.

This project discusses the use of commercially available simulation and scheduling tools to increase the efficiency of the manufacturing process based on monoclonal antibody (mAb). SuperPro Designer and SchedulePro (Intelligen, Inc) is used as a recipe based scheduling tool while VirtECS Scheduler (APC, Inc) is used as a mathematical optimization tool. The manufacturing facility of Eli Lilly and Company located in Kinsale, Ireland is modeled for this thesis. A comparison of these two tools to determine an optimal schedule is obtained. The results show detailed equipment tracking, increased scheduling flexibility, faster facility fit, real-time scheduling and automatic conflict resolution. Increasing the efficiency of the process as well as playing a significant role in day-to-day activities and therefore saving valuable employee time.

DEDICATION

I would like to dedicate this thesis to my family Mr. Chetan Prabhu, Mrs. Harshada Prabhu and sister Ms. Snehal Prabhu for all their love and support throughout my life

ACKNOWLEDGMENT

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ABBREVIATIONS

BOM	Bill Of Materials
CHT	CIP Hold Time
CIP	Cleaning In Place
DHT	Dirty Hold Time
DNS	Downstream
EOC	Equipment Occupancy Chart
GC	Gantt Chart
MEBC	Material and Energy Balance
PTM	Process Transfer Manifolds
SHT	SIP Hold Time
SIP	Steaming In Place
TP	Transfer Panels
WFC	Water For Cleaning
WFI	Water For Injection

LIST OF TERMS

Campaign: several batches of the same product scheduled sequentially

Cycle time: time to complete all the operations / activities of a given batch

Drug product: the drug which comes out of the final step in the downstream process

Drug substance: drug solution in intermediate stages

Maximum hold time: maximum idle time permitted, between two different activities operations, inside an equipment

Takt time: minimum time to start the next batch

Target prep ahead: term used in VirtECS Scheduler to start an activity, if possible, 'Target prep ahead' time before the reference activity

Titer: concentration of the target protein in the product stream of the production bioreactor

Chapter 1: INTRODUCTION

1.1. Pharmaceutical industry

Pharmaceutical industry discovers, develops, produces, and markets drugs or pharmaceutical drugs for use as medications. It may deal in generic or brand medications. They are subject to a variety of laws and regulations that govern the patenting, testing, safety, efficacy and marketing of drugs. It is also one of the most profitable industries.

Factors differentiating the pharmaceutical industry from other industries include very long product development times, large capital investments, extensive regulations and a high level of business uncertainty. Unlike other industries that constantly come out with new designs or improved models for their products, the pharmaceutical industry may seem very conservative when it comes to change. For example, a retail company's product portfolio will include many different designs and new items would launch every season. Items from last season will be considered out of fashion and obsolete. Pharmaceuticals, on the other hand, take a long time to develop and even longer to approve by the regulatory authorities.

Pharmaceutical industry products can be divided into small molecules and large molecules. Small molecules are usually chemically synthesized while large molecules or biologics are usually produced using engineered cells. In contrast to small molecules, large molecules are very complex having thousands of amino acids. Large molecules work by transporting the drug to specific locations without releasing it before reaching the target location. Therefore they are normally given through injection or infusion.

1.2. Monoclonal antibody (biologic)

Monoclonal antibodies are laboratory produced molecules made from identical immune cells that are clone of unique parent cell. mAb's consist of two regions, Fragment Antigen Binding (Fab) and Fragment Crystallizable (Fc). Fc is the tail part of an antibody that interacts with cell surface receptors. Fab is the region on an antibody that binds to the antigen. It is composed of one constant and one variable region. Based on these regions there are four types of mABs

1. Murine (-omab): they are entirely derived from murine (relating to mice) source
2. Chimeric (-ximab): the variable regions are murine while the constant regions are human
3. Humanized (-zumab): mostly derived from human source except for the part of the antibody that binds to its target.
4. Human (-umab): entirely derived from a human source

They are used as diagnostics and therapeutics in medical uses as well as used to purify components and mixtures.

1.3. Company overview

Eli Lilly and Company established on January 17, 1901, is engaged in drug manufacturing business. The company has products in two segments – human pharmaceutical products and animal healthcare products for food animals and companion animals.

The company's human pharmaceutical products include endocrinology products, neuroscience products, oncology products, immunology products and cardiovascular products.

1.4. Literature overview

1.4.1. Pharmaceutical market

Monoclonal antibody (mAb) are currently the fastest growing sector of the pharmaceutical industry (Li and Zhu, 2010). There was an increase in global sales from ~$39 billion to ~$75 billion between the years 2008 and 2013. With this growth rate, the global sales of the mAbs are likely to reach $125 billion by 2020 and $138.6 billion by 2024 (Aggarwal, 2014). Currently, monoclonal antibodies for disease patients typically cost at least $15,000 to $20,000 per year. Products for rare diseases or therapies that are customized for an individual patient often cost far more. For example, a full course of Provenge, the first therapeutic cancer vaccine and the first based on self-donating cellular immunotherapy, is projected to cost $93,000 (Fanneau, 2010). (Shaughnessy 2012) indicates the cost and complexity of the manufacturing process, increased drug complexity and risk of clinical failure (Berg et al, 2005), regulatory pressures and increasing demand (Ransohoff, 2009) as the reason behind the high cost of monoclonal antibodies. It means that there is a need to produce more efficient and lower capital intensive process which has a profound effect on the bottom line.

Such improvements call for process designs and/or revisions which are needed at early stages of process development. Biopharmaceutical Industries are preferring use of simulation and scheduling tools to assess such revisions and to experiment with various process alternatives, activities which could be time consuming and expensive to carry out in real life experiments.

1.4.2. Complexities in biopharmaceutical industries

It takes between 7-12 years for developing a new drug i.e. from research and development (R&D) to marketing approval, with cost estimates of approximately $2.9 billion (Palgon, 2014). 80-90% of these drugs fail during the development stages (Lo, 2017). Therefore it is necessary to design cost effective manufacturing process that enables the product to be produced and marketed on time, thus scheduling in such a way as to meet the demands with minimal delays especially when there are huge penalties. Additionally, uncertainties in biopharmaceutical industry makes the process more complicated against small molecules manufacturing process or semiconductor industries (Johnston, 2010). This variability could be in titers, cycle time of the unit operations, resin bed heights, yields across the unit operations and therefore it becomes difficult to understand the effect of certain minor change on the bottom line.

Regulatory constraints, particularly in cases where live organisms are used, require that additional precautions are taken with respect to facilities and equipment, such as the use of dedicated facilities and equipment, production on a campaign basis and the use of closed systems. These present a challenge with regards to facility design and process scheduling as manufacturers must overcome the complexities of area restrictions and shared resources whilst maintaining optimal scheduling.

1.4.3. Modeling of biopharmaceutical process

Potential applications of simulation tools in biopharmaceutical industries is summarized in figure 1 (Farid et al 2009, Petrides 2002). Design of the manufacturing facility should be simulated to minimize product losses in various unit operations. Scale-up, technology transfer and facility fit requires detailed study of cost expenditures, capacity evaluations

and optimal site selection which is facilitated by simulation tools. At the manufacturing level daily scheduling, debottlenecking is required for improving facility efficiency which can also be achieved. The drug commercialization process can be done efficiently and swiftly without the need for expensive and time consuming experiments.

Figure 1: The applications of simulation tools

(Koulouris, A. Siletti et al. 2007) discusses the challenges faced during scheduling, especially in biopharmaceutical industries. These challenges are because of

- The duration of a single batch from the start of upstream to the end of downstream

- Capacity constraints throughout the process

- Different batch sizes due to variability in titers

- Expiry times of various tasks for eg cleaning, steaming, buffer

- Sharing of limited equipment, utilities and other resources

- Elaborate quality control and quality assurance checks

- Automation and instrumentation related constraints

- Batch failures or lower yields

- Periodic maintenance and changeover tasks

Therefore, simulation and scheduling tools play an important role in biomanufacturing facility especially when they can handle these complexities.

1.4.4. Commercially available tools

Commercially available simulation and scheduling tools and their use in pharmaceutical manufacturing are described at length **by** (Petrides, Carmichael et al. 2014)], who in particular highlight the capabilities of finite capacity scheduling tools. Shanklin et al. (2001) evaluates two commercially available software packages (Aspen Batch Plus vl.2, Aspen Technology, Inc., Cambridge, Massachusetts and Intelligent SuperPro v3.0, INTELLIGEN, INC., Scotch Plains, New Jersey) for modelling industrial biotechnology processes. Thus, different type of software packages offer different functions which are suited to specific objectives.

The features that need to be present in simulation and scheduling tools to be able to handle the complexities in biomanufacturing facility are as follows (Koulouris, A. Siletti et al. 2007; Banks, 1998). Ease of data transfer to and from other software packages to prevent re-entering data and facilitate exporting results. Easily understood and unambiguous modeling syntax. Responsive debugger for pointing out errors in the model. Ability to assign tasks to equipment and the resources occupied by each of the task. Tracking of these resources throughout the process. Ability to assign all global as well as situational constraints to not limit the validity of the model. Real time features in scheduling to mark the progress of tasks throughout the campaign. Random variability generator, either in the package or linked externally, for sensitivity analysis. Resolving

conflicts, arising due to stochastic delays, automatically and at higher speeds. Generating standardized as well as customized reports on materials, resources, costs etc with graphs. Process simulation and scheduling software packages can broadly be divided into two types

Mathematical optimization tools: they tend to produce a feasible schedule which usually optimizes an objective function for e.g. minimize cycle time or minimize throughput subjected to various constraints. The software studies the interaction of various dependent tasks by shuffling them and chooses the best schedule. An example is using mixed integer linear programming (MILP) in GAMS to generate optimal schedule. Lakhdar (2005) concludes that even though an optimal schedule was generated it is not best suited for simulation mainly because of heavy reliance on mathematical algorithms which forces scenarios to be modeled rigidly and scheduling relies on constraints which can be better represented using discrete event simulators. While Miller et al (2010) compares the use of mathematical model to the use of discrete event simulators stating that the level of complexities that arise in discrete event simulators is large due to many equipment, tasks, and resources. Also, discrete event simulators considers tasks in chronological order and events already occurred are not touched. While mathematical model reshuffles in the timeline to generate optimal solution

Recipe based simulation tools: they do not use mathematical algorithms and therefore are computationally less expensive. They are incapable of studying interaction between successive tasks and determining the best scenario to be scheduled. Although, in recent year hybrid software packages are also available which provide a combination of these

simulation techniques. These tools which do not allow for additional programming are limited by the features which are available and therefore limiting the models validity.

Spreadsheet based tools: allow deterministic, stochastic and partial optimization using add-ons such as Crystal Ball. Due to availability of spreadsheets and online literature these are most commonly used. These tools are static in nature and any time dependencies is not considered. Additionally, complex conditions cannot be implemented which may further increase the run time.

Discrete event simulation tools: Law and Kelton (1991) describe this as the modelling of a system as it evolves over time by representing the instantaneous change in the state variables. The most common modelling elements in a discrete event simulation system consists of: Entity: which would be any stream moving from one unit operation to another. Attribute: a piece of information that describes an entity i.e. arrival time od components of unit operation. Resources: include labor, equipment, buffers. Queue: indicates the priority list
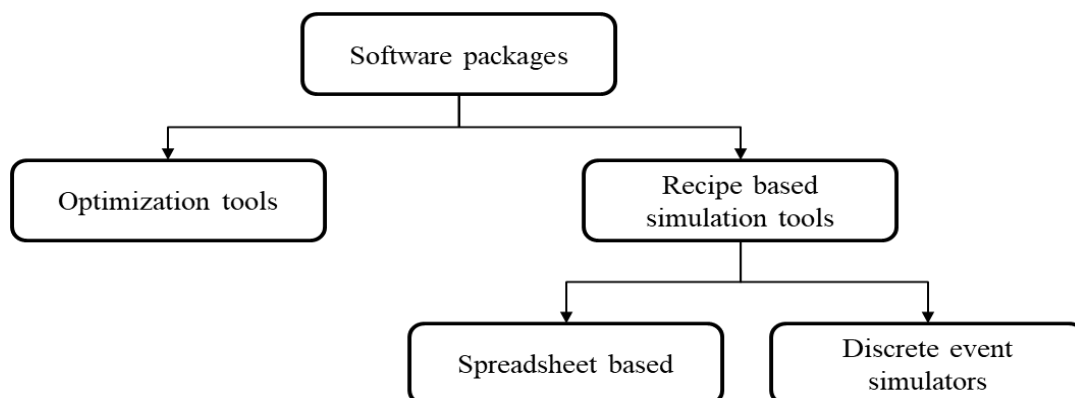
Figure 2: Classification of commercially available software packages

1.4.5. Simulation studies

When presented with a simulation problem it is advised to go through the route proposed by Banks, 1998 with steps shown in figure 2. It clearly defines the hierarchy of steps right from problem formulation to its implementation. Thus the power of these tools is not limited to simulating different scenarios but also comparing and understanding their outcomes.
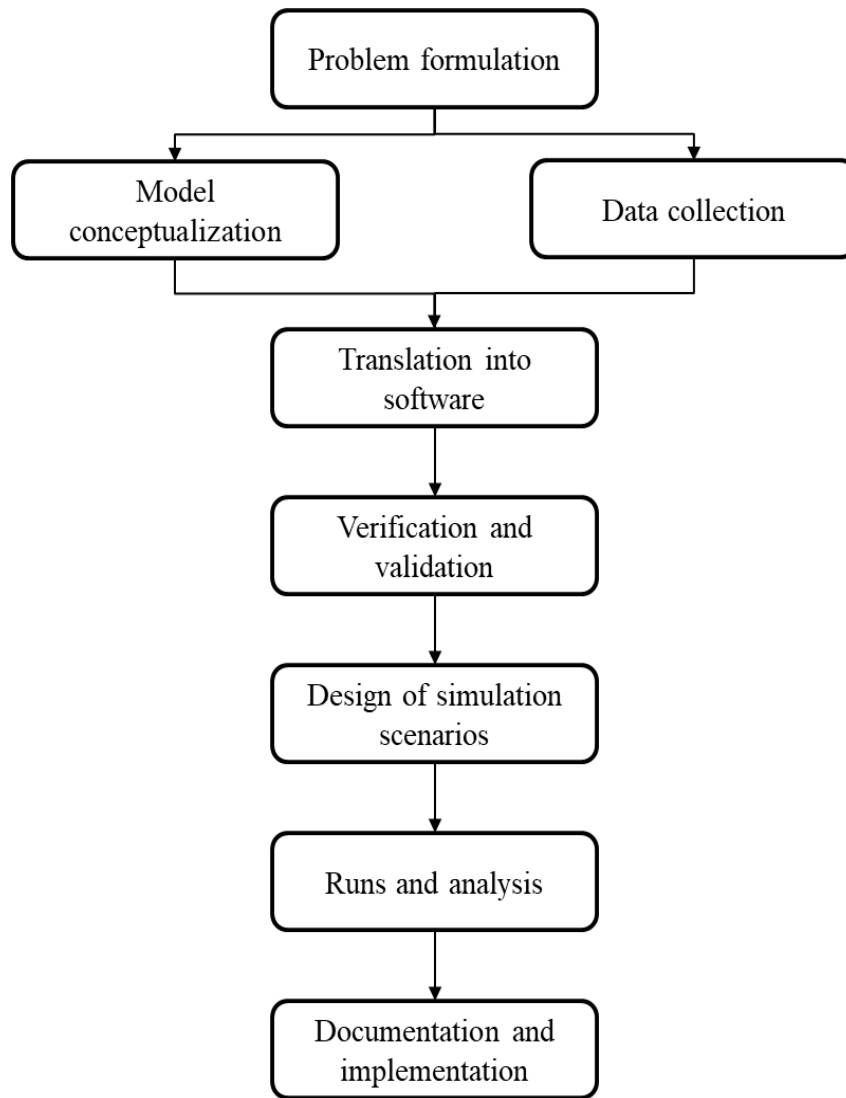
Figure 3: Hierarchy of simulation study

1.4.6. Debottlenecking the manufacturing process

Koulouris, 2014 divides the bottleneck equipment into two types: scheduling bottleneck that limits the number of batches or process cycle time and size bottleneck that limits the batch size.

$$Plant\ throughput = Batch\ size\ X\ Number\ of\ batches \dots\dots\dots\dots\dots\dots Equation\ 1$$

$$Plant\ throughput \propto \frac{Batch\ size}{Plant\ cycle\ time} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots Equation\ 2$$

$$Step\ batch\ size = Cycle\ size\ X\ \frac{Number\ of\ cycles}{Batches} \dots\dots\dots\dots\dots\dots\dots\dots\dots Equation\ 3$$

$$Cycle\ time = \frac{Process\ time}{Number\ of\ units\ available} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots Equation\ 4$$

The equipment that yields the lowest maximum batch size is the size bottleneck, which determines the maximum batch size of the entire recipe. Whereas the scheduling bottleneck is usually an equipment with the highest cycle time.

Debottlenecking strategies are summarized in table 1.

Table 1 Debottlenecking strategies

To increase plant throughput, changes that increase the batch size or reduce the plant cycle time can be effective. In general, we recommend the following strategy.

- Increase batch size until at least one cyclical step operates at 100% use capacity.

- If equipment uptime is low, try increasing the number of cycles per batch for that equipment. This may create opportunities for additional increases in batch size. A side benefit of increased batch size is the reduced cost for quality control (QC) and quality assurance (QA), which depend on the number, not the size, of the batches.

- If a process operates at its maximum batch size, work to reduce plant cycle time by eliminating time bottlenecks. Long process steps and equipment sharing cause time bottlenecks.

- If bottlenecks are created by equipment sharing, install extra equipment that reduces the sharing. The size of the new equipment should be chosen to create opportunities for batch size increases (basing the equipment size on the most demanding step). Rearranging the order in which equipment is used (for shared equipment) can create opportunities for reducing cycle time and sometimes for batch size increases.

- If the time bottleneck is caused by a step that has a very long cycle time, new equipment should be operated in a staggered mode based on the cycle time of the next time bottleneck.

- If the time bottleneck is caused by equipment, it can sometimes be eliminated by moving secondary operations from bottlenecked to nonbottlenecked equipment (1). For instance, instead of heating material in a vessel, heating can be done using an external heat exchanger during the charge and transfer of material into the vessel.

- If bottleneck analysis suggests buying new equipment, the final purchase decision should be based on an evaluation of overall project economic criteria, not simply on throughput considerations.

Reference

(1) Minnich, T.M., "Use Process Integration for Plant Modernization," *Chem. Eng.*, 70–76, (August 2000).

1.5. Manufacturing process description

The project is focused on modeling the entire process of Product A in the manufacturing facility IE-43. Facility IE-43 is considered because it has the largest complications from all other established facilities in Eli Lilly. Additionally, Product A is considered due to multiple cycles of protein affinity chromatography which adds to more complications. The manufacturing process is divided into upstream and downstream (or purification)

Upstream: The cell culture process begins with thawing cells obtained from the working cell banks. The volume of cell culture is increased through series of cell transfer depending on cell density when the volume exceeds to the limit where it cannot be held in flasks, expansion is achieved using seed bioreactors and is stopped at the production bioreactor. An antibody with a given titer is produced in the production bioreactor. Following harvest of the production bioreactor, the biomass is separated using a series of filtration and centrifugation units. It is then transferred for further purification to the downstream process.

Downstream: Product A purification process begins with Protein Affinity capture chromatography (ProA). It captures the protein away from process related impurities like media components, DNA as well as process additives. Followed by viral inactivation which inactivates the viruses sensitive to pH and also neutralizes the process intermediate suitable for further processing. The tangential flow filtration (TFF-1) exchanges the buffer suitable for the next unit operation anion exchange chromatography (AEX). AEX further reduces process related impurities and also some viral clearance is achieved. Followed by additional viral clearance through viral filtration steps. Tangential flow

filtration (TFF-2) then exchanges to the appropriate buffer necessary for final drug substance preparation and also concentrates the antibody to the appropriate range. Finally, the formulation is completed and the drug substance is collected in bottles before additional viral filtrations steps.

Figure 4 shows the block flow diagram of the overall process.
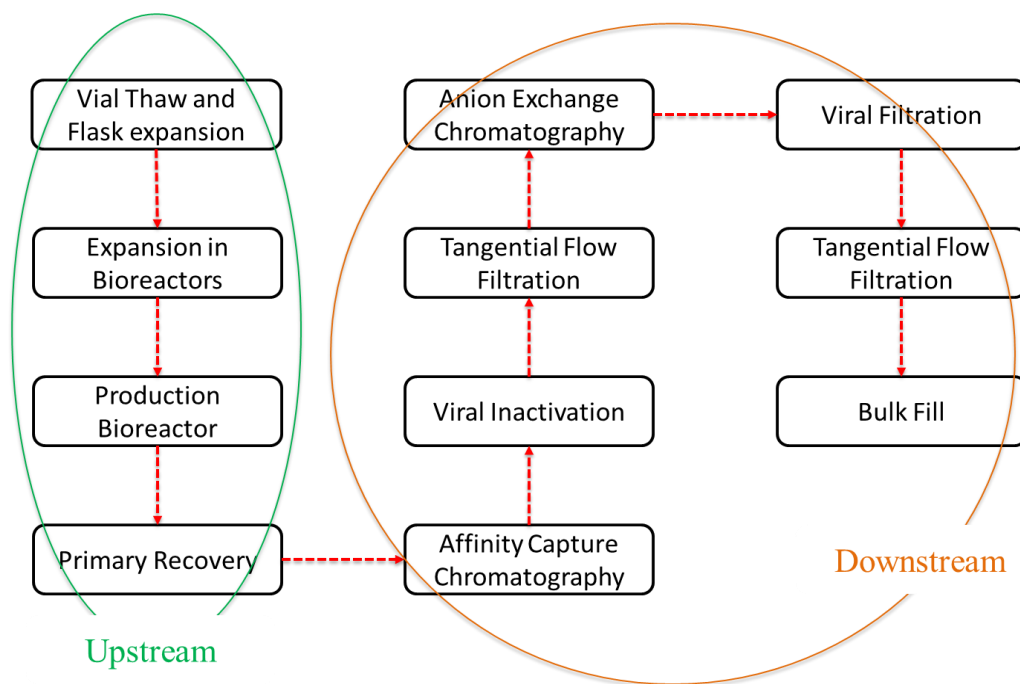
Figure 4: Manufacturing process of product A

Chapter 2: PROBLEM STATEMENT

2.1. Project Objectives

The primary goal of the project is to produce a detailed flowsheet model of the manufacturing process of a specific biologic with the ability to support day-to-day scheduling. Other goals include:

- Estimating the theoretical cycle time and estimating the bottleneck of the process
- Detailed material balance across the entire manufacturing process
- Predicting changes in the output based on the changes in the input streams
- Tracking resources
- Evaluating production line capacity
- Providing cost analysis
- Process improvements

This model is then compared with the one generated using mathematical optimization tool

2.2. Project scope

The model will encompass the entire manufacturing process i.e. both upstream and downstream process. The scope of the project is to produce a model with the capability of equipment time utilizations and enable the simulation of different scenarios of the bio-manufacturing process. The model does not consider

- QC testing between operations
- Effective management of raw materials
- Labor shift patterns
- Detailed changeover plans and maintenance
- Mechanistic modeling

Chapter 3: SOFTWARE SELECTION

Several recipe based scheduling tools were compared (APPENDIX B). Table 2

summarizes the features that can achieve the desired objectives along with their modeling

level of difficulty, of two primary candidates

Objectives	SuperPro/SchedulePro	RTMS (BioG)
Partial optimization	Min takt time	Min takt time
Stream-wise Mass balance	Yes	Yes
Debottlenecking	Yes	Yes
Sensitivity analysis	Yes	Yes
Resources tracking	Yes	Yes
Scheduling with capacity constraints	No	Yes
Facility fit	Yes	Yes
Process variability	Yes	Yes
Capacity analysis	Yes	Yes
Cost analysis	Yes	Yes

Level of difficulty		
Hard	Moderate	Easy

Table 2: Comparison between two potential software

3.1. Software selection criteria

Static versus dynamic: static models are usually spreadsheet-based and are time

invariant. Real-time control is not possible and scheduling is purely based on intuitions or

past experiences. While dynamic models consider time-dependent changes.

Accuracy: In order to get accurate results the software should be able to incorporate all the necessary constraints of the facility and should have minimum assumptions. The assumptions made should not compromise any constraints related to the manufacturing process and facility.

Easy to implement: The long term goal of this project is to replace the currently used tool. In order for the new software to be readily accepted across the facility, the learning curve should not be steep.

Adaptability: The same facility is used for manufacturing different products. Each of these products may have different parameters for their operations. Thus the model should be easily replicated and should take less time to build for these products and predict changes before actually running the batches.

Cost: The price should be reasonable and within the budget allocated to the modeling team.

Finally, SuperPro Designer/SchedulePro (Intelligen, Inc. NJ USA) were chosen as the recipe based scheduling tools. To compare the results VirtECS scheduler (Advanced Process Combinatorics, Inc. IN USA) was chosen as the mathematical optimization tool.

3.2. **Data sources**: the information input to all the models come from various data

sources. A summary of data sources is provided in the table 3

Information on	Source
Batch throughput	Excel
Run rate	Process engineers
Equipment assignment	PSQ plan
Equipment assignment	PFD, P&ID
Operation timings	AMAL
Operation timings	Process engineers
Scheduling rules	Excel
Scheduling rules	Process engineers

Table 3: List of sources for various information

Chapter 4: METHODOLOGY

4.1. Activity / operation classification

All the activities/operations which occur inside any equipment, throughout the process, can be divided into three types

Preparation activities/operations: it includes cleaning using buffers, setups, manual checks, etc. They are usually completed before the product enters the equipment. For eg. SIP, washing with WFC, etc.

Product activities/operations: it includes everything that acts chemically or physically with the drug substance. For eg. buffer exchange in TFF, protein formation in bioreactors, virus removal in filtrations etc.

Cleaning activities/operations: it includes everything that occurs after the product has left the equipment which may include cleaning using buffers, steam and equipment disassembly. For eg. CIP, post-use wash with buffers, etc.

4.2. Model assumptions

The list of assumptions that were considered while modeling in any software

- The activities/operations once started, cannot be interrupted and should go to completion. If certain activity/operation are to be separated by a time gap they are represented as two separate operations/activities and scheduled accordingly.

- The level of detail in activities/operations depend on the objectives that need to be achieved from the software. For eg CIP can be represented as a series of small wash

steps that need cleaning solutions or as a single CIP that take aggregate time and cleaning solutions of each of these small steps.

- All buffer hold vessels are filled as-soon-as-possible or just-in-time. No unnecessary time gaps are incorporated

- No multi-tasking is allowed except for cases where conditions for multitasking are met. For eg. buffer hold vessels cannot transfer as well as receive buffer simultaneously.

- Randomness in the process is considered very small as compared to the actual duration of the process and is therefore ignored

- Expiry times of buffers have not been considered but it is fair to assume that they do not expire in the hold vessels since their refilling time is very less than their expiry time.

- Cleaning activities/operations like CIP and SIP do not assume the worst possible scenarios where they fail to meet the cleaning specifications and have to be cleaned for longer periods again

- Materials like WFI; utilities like power, steam etc. are available infinitely and do not act as a scheduling constraints

- Every activity/operation requires an operator throughout its duration of execution. Operator shifts have not been considered. Also, the specified operators work with 100% efficiency and are only unavailable during the facility downtime.

- Equipment changeover cleanings and column setups which usually occur just before the first batch of the campaign is not considered.

- Except for the buffer preparation, other activities/operations in the upstream and downstream process are identical throughout the campaign.

4.3. Modeling in recipe based simulation tool (SuperPro Designer)

The manufacturing process or the recipe of Product A has been modeled in SuperPro Designer (Intelligen, Inc. NJ USA). The model has the following 12 sections

I. Flask expansion
II. Seed Bioreactor
III. Production Bioreactor
IV. Primary recovery (PR)
V. Protein Affinity chromatography (ProA)
VI. Viral inactivation (VI)
VII. Tangential flow filtration (TFF-1)
VIII. Anion exchange chromatography (AEX)
IX. Nano filtration (NF)
X. Tangential flow filtration (TFF-2)
XI. Bulk fill
XII. Buffer Preparation
XIII. Transfer panels

Each section has various unit operations. Each unit operation is defined by a unique procedure in the model. Each procedure, in the model, has to be assigned an equipment where the unit operation is performed. Thus, different procedures can occur in the same equipment. Various tasks are performed in this equipment which becomes the operations inside the procedure for the model. For e.g. the 'Seed bioreactor' section has the bioreactor B-101 (B-101 equipment assigned to procedure P-101). It has several operations like SIP, Media in, Media check, Bioreaction, CIP occurring in the procedure P-101 which also occupies the equipment B-101.

The model is provided with the following information:

I. For each section

- The various procedures assigned to the section
- The sequence of these procedures

II. For each procedure

- The various equipment where the procedure happens (different or same equipment for different procedures)
- The mode of operation of these equipment (series or staggered)
- The number of cycles of each procedure (how many times the procedure is repeated per batch)

III. For each operation

- The input and the output stream of the given material, if there is material transfer
- The amount of material required and the duration of operation
- The amount of labor required
- The auxiliary equipment required, if any (equipment, utilities)
- The relative time of operation with respect to other operations

IV. For each equipment

- The mode of operation (design or rating mode)
- The different procedures which share the given equipment
- Purchase cost of the vessel (material of construction)

The sequence of operations in a procedure is modeled such that the process time is minimum. That is all the operations are tightly packed. For e.g. the operations of a bioreactor include SIP, MEDIA IN, MEDIA HOLD, REACTANT IN, REACT, PRODUCT OUT and CIP. The operation REACTANT IN (transfer of product stream from the previous unit operation which acts as a reactant for this reaction) is started as

soon as the previous unit operation is finished. All the operations which precede

REACTANT IN are scheduled backward. Operation MEDIA HOLD is finished just

before the start of REACTANT IN. MEDIA IN is finished just before MEDIA HOLD

and SIP just before MEDIA IN. All other operations which succeed REACTANT IN

are scheduled forwards. Operation REACT is started as soon as operation

REACTANT IN is finished, immediately followed by operation PRODUCT OUT

and CIP. This method is followed throughout the model for all operations.

The binding capacity of resin used to capture protein (in ProA) is 35gm of protein/L

of resin. Thus for a given column dimensions there isn't enough resin to capture all

the protein in the inlet stream. Thus, to capture almost all protein ProA is run multiple

times per batch. But the CIP and SIP of the skid are done only once per batch. To

capture this constraint the unit operation ProA is divided into three different

procedures occurring in the same column. The first procedure has the SIP operation

which is done once per batch. The second procedure has the column operations from

LOAD to REGEN, which are done multiple times. Finally, the CIP is in the third

procedure which is also done once per batch.

The downstream process heavily utilize buffers for various unit operations. Each

buffer has its own dedicated hold vessel. Since mass is conserved, the input to these

hold vessels is the output to the process. In other words, these hold vessels track the

amount of buffers consumed by the process per batch. These buffers are usually

transferred from their hold vessels to their respective unit operation using transfer

panels. These transfer panels have their own SIP and CIP after every transfer. To

account for this constrain, transfer panels were added as separate procedures. They

are occupied whenever there is a buffer transfer. This also prevents any operations to happen simultaneously.

A sample model of the recipe of Product A in SuperPro Designer is attached in APPENDIX A.

Overall, the recipe of product A has 13 sections, around 450 procedures, and 1000 operations.

4.4. Modeling in recipe based scheduling tool (SchedulePro)

The recipe was exported to SchedulePro from SuperPro Designer. Certain changes had to be done to make it compatible with SchedulePro.

Buffer preparation: unlike in SuperPro Designer where the worst batch is modeled and repeated over the campaign, in SchedulePro all the different batches can be modeled and their interaction can be seen (APPENDIX B). Since buffer preparation operations do not occur every batch they do not have to be a part of the same recipe as that of Product A (which is repeated every batch). Different filling frequencies can be specified for each of the 18 buffers by assigning them their own recipes.

Facility downtime: the facility remains operational only for 17 hours. For the rest 7 hours none of the operations can be started but labor-intensive operations which are started during operational time can be finished during this period. These 7 hours constitute the facility downtime. This facility downtime could be specified using certain in built features in SchedulePro. In SuperPro Designer every operation is relative to every other operation and not relative to the calendar time. Thus, adding facility downtime, in SuperPro, becomes almost impossible without compromising certain features.

Operation flexibility: operations can be delayed up to a certain maximum limit (flexible shift) due to various reasons like unavailability of labor, auxiliary equipment, materials, facility downtime etc. If a resource is unavailable for a specific operation then the next batch need not be delayed rather that operation could be scheduled later. For e.g. DHT (maximum time the equipment can stay without being CIP'd) of an equipment can be added as flexible shift for its CIP operation. Thus CIP will be scheduled within the DHT whenever resources like CIP skid is available. Similarly, SHT (the expiry time of SIP of equipment) could be added as the flexible shift for SIP of equipment.

Overall the model consists of 1 process recipe (upstream and downstream), 18 Buffer preparation recipes, around 100 procedures and 500 operations

Campaign scheduling: 13 batches of product A are scheduled instead of 12. Batch 13 is identical to batch 1 in all ways except that it captures the interaction of the previous batch (batch 12) which batch 1 does not. The cycle time of the process (takt time) is specified along with the start date. For the rest 18 buffer preparation recipes, the same process is followed with the maximum batches set to 13. But since buffer preparations are not done before every batch, a trigger situation is mentioned to start preparation of specific buffer before a specific batch. Usually, these recipes are triggered whenever the buffer in the hold vessel reached 0% of its working volume. In the actual facility, the volume never drops to 0% of its working volume. There is always some make-up volume of buffers which is left (due to variability in the process) and later drained off before refilling. But in the model, it is safe to assume that every batch requires the same amount of buffer and is refilled whenever the volume drops to 0%.

4.5. Data transfer using excel spreadsheets

For the model in SuperPro Designer, Visual Basic for Applications (VBA) is used to transfer data from excel spreadsheet. All the operating conditions of the process, material balance constraints, scheduling information could be transferred. Similarly, data can be collected from the model for further analysis.

For the model in SchedulePro, only a certain type of data can be transferred. Data such as the equipment allocation to procedures, operations allocation to procedures, the duration and the resources (auxiliary equipment, labor, utilities, etc.) occupied by each of these operations. Buffers consumed or released cannot be transferred. Also, all equipment must be registered in the model before assigning them to different procedures.

4.6. Modeling in mathematical optimization tool (VirtECS Scheduler)

The manufacturing process of product A is divided into two recipes – Upstream recipe and downstream recipe. They are further divided into stages.

I.   Stages in the Upstream recipe

- Vial Thaw
- Flask expansion (each passage has its stage)
- Seed bioreactors (each passage has its stage)
- Production bioreactor
- Primary recovery

II.   Stages in the Downstream recipe

- Starting buffer volumes
- Protein Affinity Chromatography (ProA)
- Viral Inactivation (VI)
- Tangential Flow Filtration -1 (TFF-1)

- Anion Exchange Chromatography (AEX)
- Nano filtration (NF)
- Tangential Flow Filtration -2 (TFF-2)
- Bulk Fill

In each stage, activities are defined. Each activity must have an activity name, the equipment where the activity occurs, the duration and the sequence of the activity. Each activity can also consume buffer, occupy resources, use WFI and hold auxiliary equipment.

Buffer preparation: The software needs to keep track of buffer volumes used by the process to schedule the buffer preparations. Thus, the amount of buffer that can be prepared in the preparation vessel and is consumed by unit operations has to be mentioned. The software is intelligent enough to determine if the volume of buffer in hold vessel is adequate for the buffer needs of the next activity. If not then the remaining buffer in the hold vessel is drained and refilled. Initially, all hold vessels are considered empty and therefore all buffers are prepared before the first batch. In order to adjust the starting volumes of the buffer in the hold vessels (APPENDIX B), a separates stage 'Starting buffer volume' is modeled. This stage occupies negligible time and is scheduled only once before the start of downstream of the first batch. It consumes a certain amount of buffers such that the remaining volume left in the hold vessels is equal to the appropriate starting volume.

Facility downtime: there is no specific option to specify the operational time of the facility but resources can be allocated to prevent activities from scheduling in facility downtime. This specific resource is available infinitely during the operational time but not available during the facility downtime. Activities that are entirely run during the

operational time occupy this resource for their entire duration, while the activities that can start during the operational time and run through the downtime can use this resource only for part of their duration.

Scheduling flexibility: the software can add delays between activities if any resources or auxiliary equipment is unavailable. Activities that should occur sequentially without any delays are lumped together with their aggregate time. For e.g. various buffer flushes are lumped together as a single CIP activity which takes the aggregate time of all flushes. CHT (expiry time of CIP after which the equipment has to be CIP'd again), DHT (maximum time after the equipment is done processing, should be CIP'd), SHT (expiry time of SIP after which the equipment has to be SIPd again) can be explicitly specified for each equipment.

Overall there are 25 stages and 200 stage activities

Chapter 5: RESULTS AND ANALYSIS

5.1. Results from recipe based simulation model (SuperPro Designer)

Note: these results lack some information considered in Part 2 and therefore may not be the desired results. They should only be viewed for basic ideas

With the model built in SuperPro Designer, the sequence of operations can be viewed from the operations Gantt chart. Gantt charts have all the operations on the y-axis and time on the x-axis (Figure 5). It tells the relative start, relative end and the duration of each of the operations by occupying a time slot in the chart. Additional information on batch time, cycle time (takt time), longest procedure, bottleneck equipment, maximum batches in a year, etc. could be obtained by viewing the scheduling summary. To visualize the effect of bottleneck equipment, the equipment occupancy chart for several batches was generated. Equipment occupancy charts have equipment on the y-axis and time on the x-axis.

As seen from the equipment occupancy chart (Figure 6) that even though the longest procedure (production bioreactor) takes several weeks the next batch does not wait for weeks to start. This is because of the fact that there are production bioreactors arranged in staggered mode (multiple production bioreactors are present). Had there only been one production bioreactor the next batch could only be started after the bioreactor finished its processing. Thus, a new production bioreactor is used from this staggered set for the next batch. It is also observed that the bottleneck equipment is not the production bioreactor but one of the seed bioreactors. The software determines the bottleneck equipment as the equipment with the least idle time. The cycle time (takt time) is the cycle time of the bottleneck equipment. That is the next batch is only started after the bottleneck

equipment is available for use. Thus the batches are symmetric across the campaign as can be seen from the equipment occupancy charts.

Various resources can be tracked using charts (Figure 7). Resources may include materials entering and exiting the process, labor, utilities and auxiliary equipment demands.
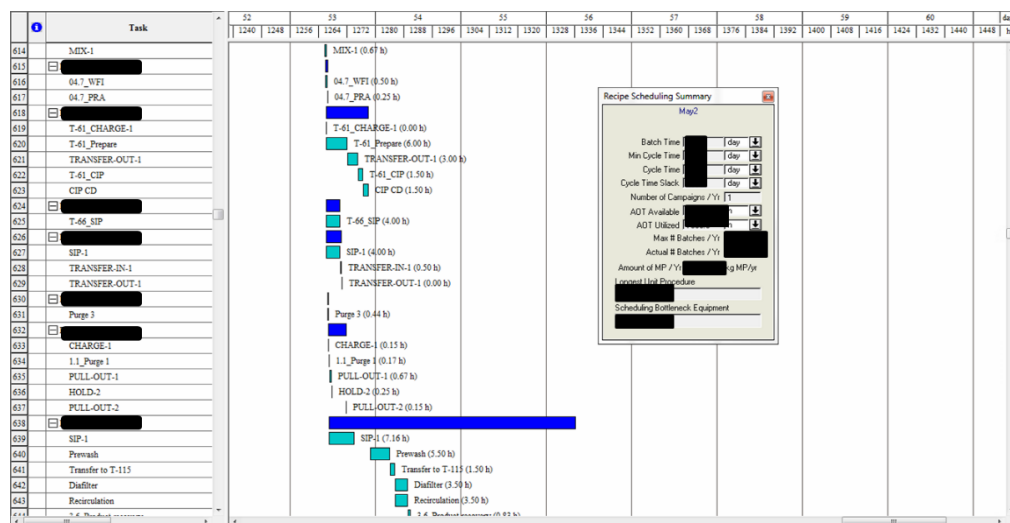
Figure 5: Gantt chart of the overall process in SuperPro Designer
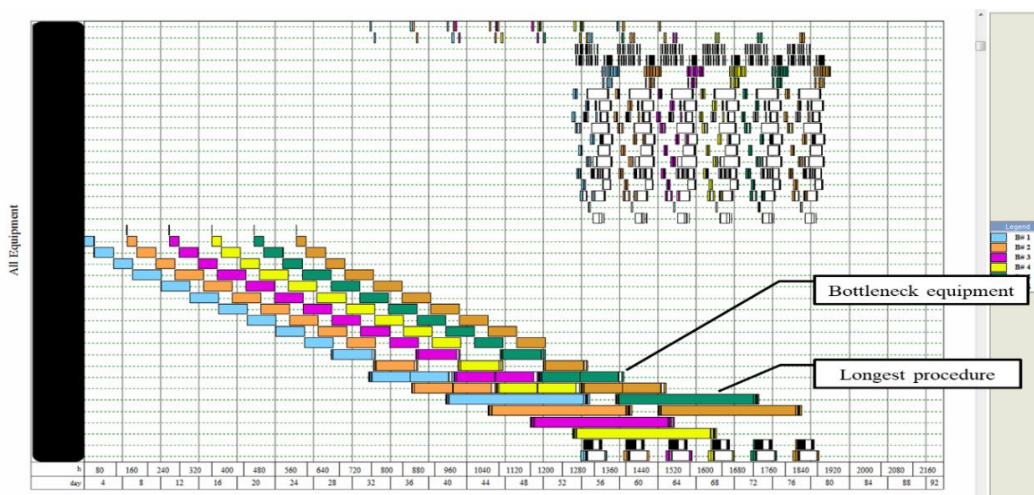
Figure 6: Equipment occupancy chart of the overall process in SuperPro Designer
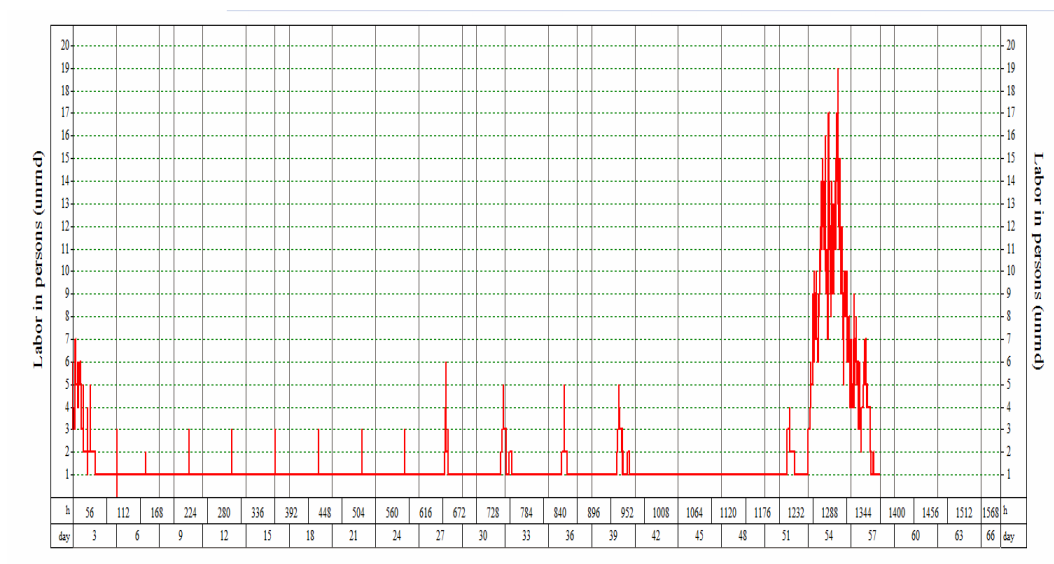
Figure 7: Chart tracking labor in SuperPro Designer

In addition to tracking of various resources, overall raw material requirements with compositions in each individual stream can also be calculated. This provides information for verifying results related to material transformation, liquid or solid waste generation, emissions, equipment capacity utilizations, etc. Figure 8, 9 shows the requirement of raw materials throughout the process per batch and yearly basis.

Material	kg/yr	kg/batch	kg/kg MP
	64,204	1,035.56	1.22
	471,075	7,597.99	8.96
	38,118,915	614,821.20	724.87
	308	4.97	0.01
	650,636	10,494.13	12.37
	1,653,911	26,675.98	31.45
	925,075	14,920.56	17.59
	8,032,735	129,560.24	152.75
	1,031	16.63	0.02
	2,473	39.89	0.05
	0	0.00	0.00
	12,648	204.00	0.24
	695,236	11,213.48	13.22
	13,888	224.00	0.26
	727	11.73	0.01
	172,689	2,785.31	3.28
	671,529	10,831.11	12.77
	1	0.01	0.00
	449,053	7,242.79	8.54
	360,555	5,815.40	6.86
	79,785	1,286.86	1.52
	514,599	8,299.99	9.79
	568,022	9,161.64	10.80
	142,102	2,291.96	2.70
	153,711	2,479.20	2.92
	124,143	2,002.31	2.36
	816,636	13,171.55	15.53
	138,944	2,241.03	2.64
	76,593	1,235.37	1.46
	59,471	959.21	1.13
	486,803	7,851.66	9.26
	20,977	338.35	0.40
	114,992,962	1,854,725.19	2,186.70
	1,230,802	19,851.65	23.40
	1,604,760	25,883.22	30.52
TOTAL	173,306,999	2,795,274.17	3,295.60

Figure 8: Raw material consumption by the entire process in SuperPro Designer

Flask Expansion

Material	kg/yr	kg/batch	kg/kg MP
	826,955	13,337.99	15.73
	0	0.00	0.00
	1,580	25.48	0.03
	110,392	1,780.51	2.10
	3,296,463	53,168.76	62.69
	370,861	5,981.63	7.05
	38,545	621.69	0.73
TOTAL	4,644,796	74,916.06	88.33

ProteinA Chromatography

Material	kg/yr	kg/batch	kg/kg MP
	111,014	1,790.55	2.11
	565,581	9,122.27	10.76
	294,839	4,755.46	5.61
	79,785	1,286.86	1.52
	514,599	8,299.99	9.79
	142,102	2,291.96	2.70
	153,711	2,479.20	2.92
	10,952,565	176,654.28	208.27
	859,941	13,870.02	16.35
TOTAL	13,674,137	220,550.59	260.03

Viral Inactivation

Material	kg/yr	kg/batch	kg/kg MP
	1,031	16.63	0.02
	20,977	338.35	0.40
	5,771,666	93,091.39	109.75
TOTAL	5,793,675	93,446.37	110.17

TFF intial

Material	kg/yr	kg/batch	kg/kg MP
	154,215	2,487.33	2.93
	486,803	7,851.66	9.26
	5,683,135	91,663.46	108.07
	416,346	6,715.26	7.92
TOTAL	6,740,498	108,717.71	128.18

Figure 9: Section wise consumption of raw materials in SuperPro Designer

Economic analysis: accurate project cost analysis (Figure 10) and economic analysis can be done and decisions could be made either to establish a new facility or retrofit the existing. Since the existing facility is already established the summary of annual operating costs and the contribution of each can be obtained.

Cost Item	$	%
Raw Materials	7,177,000	31.14
Labor-Dependent	8,551,000	37.10
Laboratory/QC/QA	1,283,000	5.56
Consumables	5,637,000	24.46
Waste Treatment/Disposal	373,000	1.62
Utilities	28,000	0.12
Advertising/Selling	0	0.00
Running Royalties	0	0.00
Failed Product Disposal	0	0.00
TOTAL	23,048,000	100.00

Figure 10: Annual operating cost summary

5.2. Results from recipe based scheduling model (SchedulePro)

The scheduling recipes can be visualized using the Gantt chart similar to the one

generated by SuperPro Designer as can be seen in figure 11. The chart can be opened in

layers and viewed with recipe specific or procedure specific or operation specific details.

Unlike the Gantt chart in SuperPro which only captures a single batch, the Gantt chart in

SchedulePro captures all the unique batches and the interactions with operations of the

successive batch.

Figure 12 shows the equipment occupancy chart of the process. 13 batches of Product A

were scheduled along with their buffer preparations activities. Grey shaded region

represents the facility downtime while the white shaded region represents the operational

time. Each batch is represented by a different color. Filter functions can be used to focus

on a specific section like upstream, downstream, buffer preparation, or a specific type of

equipment like CIP skids, preparation vessel or a specific type of operations like CIP,

SIP.
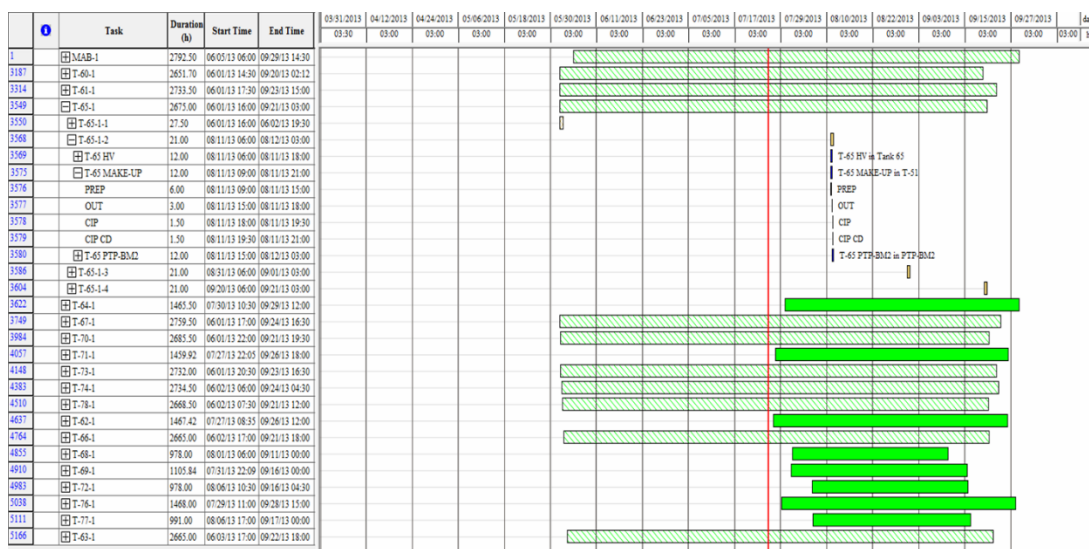
Figure 11: Recipe Gantt chart in SchedulePro
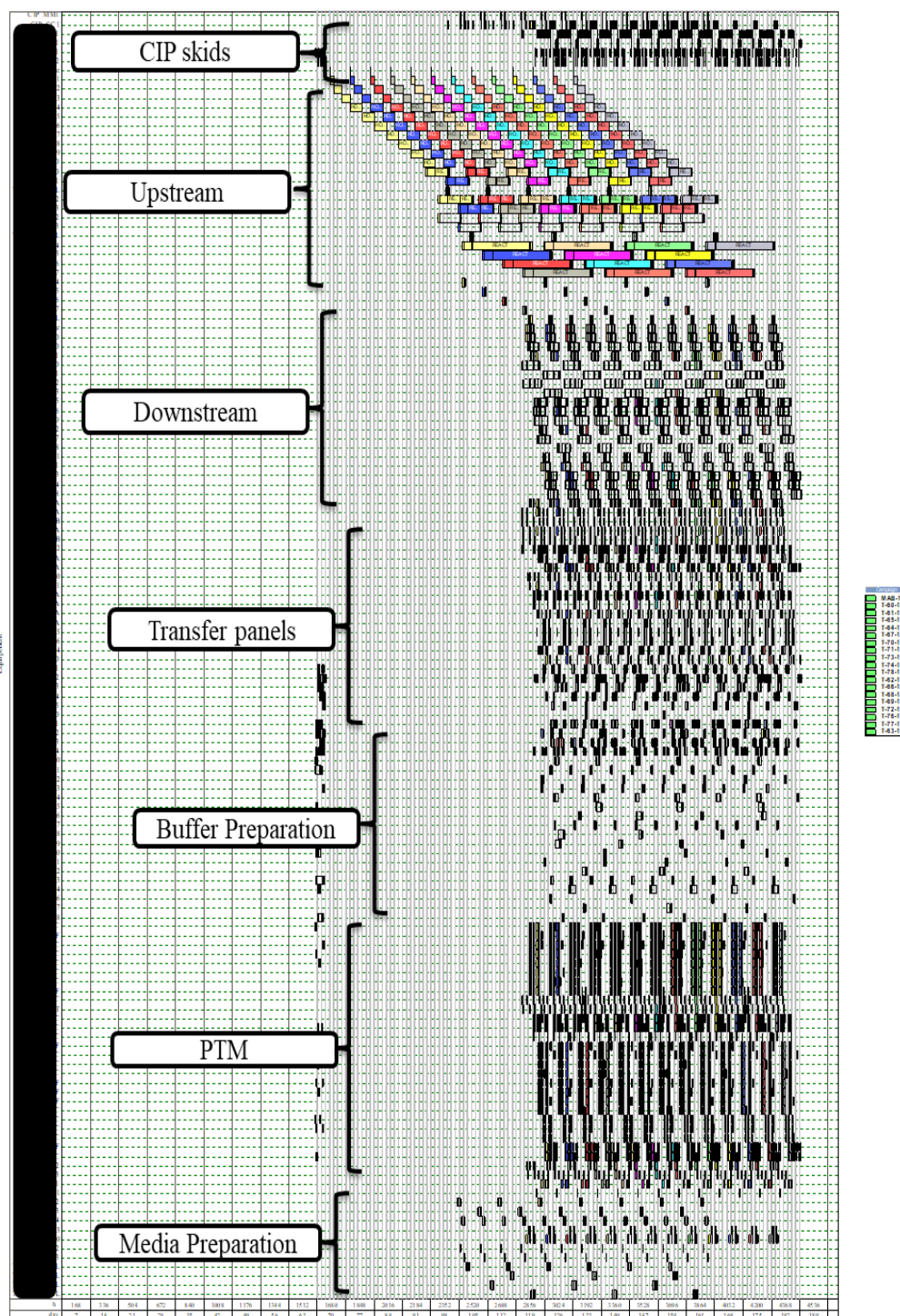
Figure 12: Equipment occupancy chart in SchedulePro

Real time control:

In a manufacturing environment in order to distinguish between past and future operations current time concept is used. The figure 13 shows the current progress of operations. The red vertical line represents the current time which can be manually set or synced with the calendar time. Based on the position of the red line operations are divided into three types – completed (filled with crossed lines), ongoing (filled with slant lines) and not started (filled solid).

This progress tracking of activities helps in real-time monitoring of the process which cannot be achieved from the current spreadsheet schedule. Any stochastic delays can be incorporated by changing the operation time based on the current time vertical line. Conflicts due to equipment, resources, utilities, facility downtime can arise with operations that are not started while incorporating these stochastic delays. The conflict resolution features automatically resolves these conflicts by delaying operations within feasible limits, swapping between vessels and reschedule all further operations within minutes.
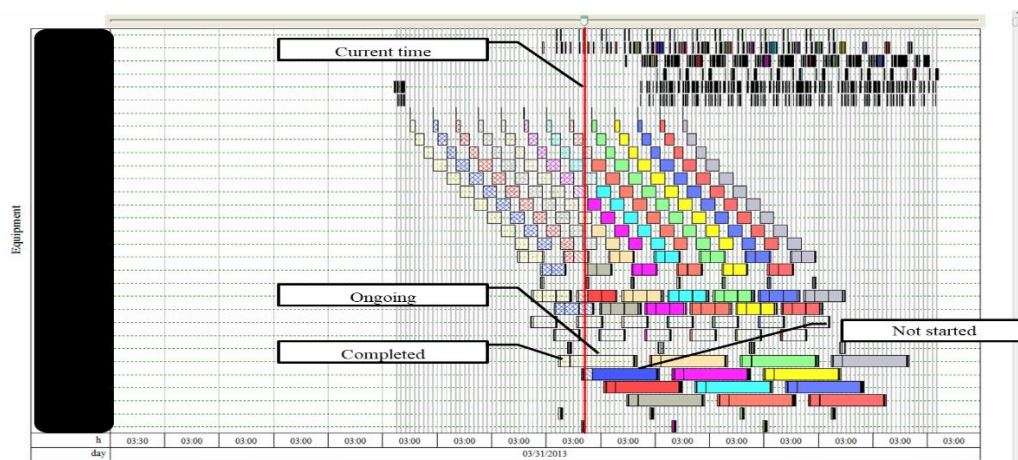
Figure 13: Real-time control in SchedulePro

Utility system sizing: WFI is used as a buffer for various unit operations, washing material in CIP operations, the source of steam in SIP operations. This WFI is transferred across the equipment using a WFI system. These systems should be sized in such a way that the demands of the facility are met. The system consists of three parts – still which generates distilled water, surge tank which holds the WFI and circulation loop which transfers WFI to the process. The figure 14 shows the consumption of WFI across the process. The chart has the following components: instantaneous demand (shown by red line), average demand over a certain time interval (blue line) and cumulative average demand over a certain time (green line). The largest value of the instantaneous demand is the pumping capacity, the largest value of average demand gives the still rate and largest value of the cumulative demand gives the surge tank size. If the time interval is reduced then the tank size is reduced while the still rate is increased. Thus there is a tradeoff between tank size and still rate. These values are calculated and compared with the existing WFI systems.

Resource management: The same chart can be used for instantaneous tracking of inventory levels in the buffer hold vessels. The figure 15 shows the inventory level of one of the buffers. The green horizontal lines show the limits on the buffer hold vessel. The blue line shows the instantaneous amount of buffer in the hold vessel. The brown and green lines represent the discharging and charging flow rates. These charts are also useful for detecting any violation in constraints. Resources like labor, utilities can be traced back to determine their utilization levels so that they can be assigned efficiently during high levels of demand.

Figure 14: WFI consumption rates

Figure 15: Buffer consumption rates
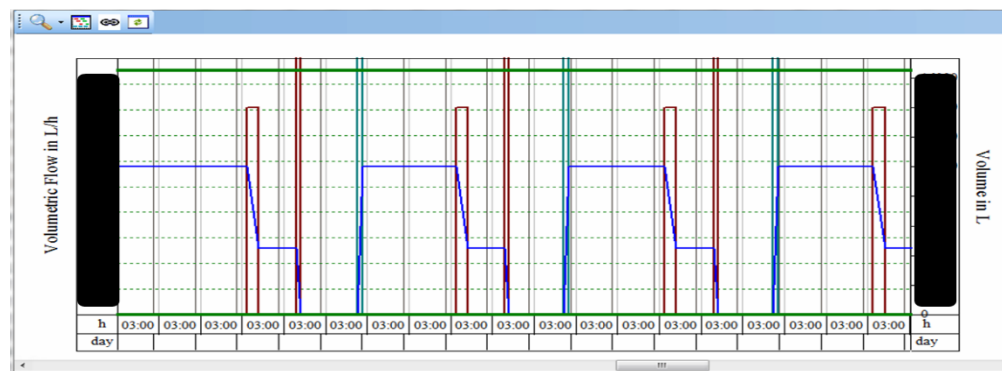
Equipment occupancy times:

The figure 16 shows the equipment time utilization chart. Utilization is counted as the time that the equipment is occupied during the selected time span. This chart is useful in determining the effectiveness of each equipment. That is the equipment after processing and waiting for CIP may remain idle due to unavailability of CIP skid but is still occupied because the operation can only occur after its CIP is completed. This leads to defining three terms

% occupied – total (blue bar): percentage of time in the scheduling horizon that the equipment is occupied by procedures. I.e. time from preprocess SIP to post process CIP.

% occupied – busy (orange bar): percentage of time in the scheduling horizon that the equipment is occupied by operations. I.e. aggregate time of all operations

% occupied – idle (pink bar): the percentage of scheduling horizon during which the equipment is reserved by procedures but not performing any operations
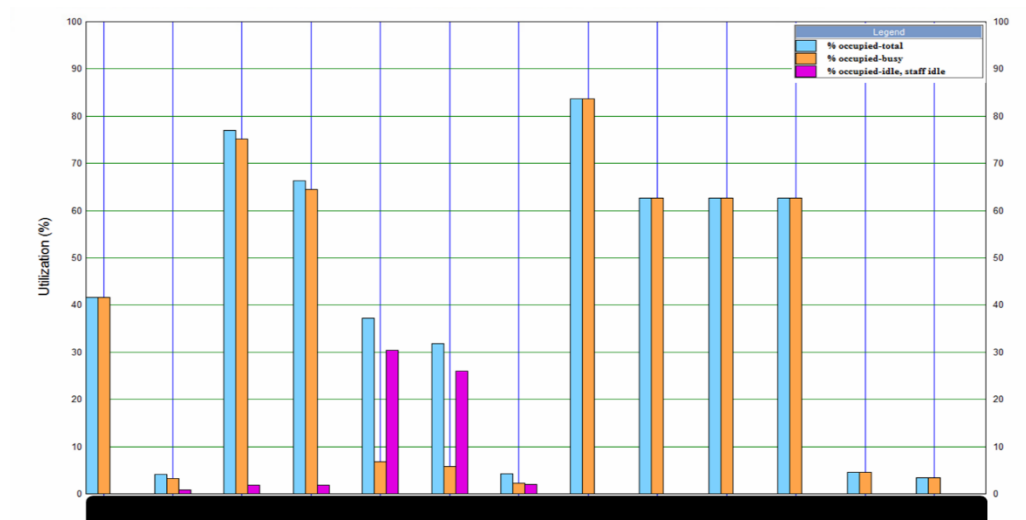
Figure 16: Equipment occupancy times

5.3. Results from Excel

Sensitivity analysis: A sensitivity analysis is used to test the robustness of a system to variability. For the mAb process one of the key variable is the split ratio, that is, the number of cycle per batch through the protein capture column. The reason for this is that the split ratio or the number of cycles is based on the following equation:

$$\text{Split Ratio} = \frac{(\text{Titer x Production bioreactor volume x Yield})}{(\text{BC of protein capture column x Protein capture column volume})}$$

where BC = binding capacity. As the titer increases the number of cycles or the split ratio must also increase if the column parameters remain constant. However if that ratio is limited then the capacity of the column becomes limiting with the percentage of product binding with every column volume decreasing as the titer increases i.e. with increase in titer, a greater percentage of product cannot bind and flows through. This affects the overall process throughput.

Further parameters which could also show impact on the % processed value: yield, column dynamic binding capacity and column volume which is determined by height and diameter. Failure rate or the contamination rate is also considered. The base case scenario assumes that there is no failure within the process however this is actually inaccurate. A certain percentage of failure is present in any new process and therefore must be captured. It can be assumed that the failure rate of this facility will be in the order of around 4% for entire process.

The input parameters used are summarized in table

Parameter	Base value	Change
Binding Capacity		±50 %
Titer		±10 %
Failure rate		±50 %
Split ratio		±20 %
Column height		±10 %
Column diameter		±10 %
Equipment yield		±5 %

Using the parameters stated in Table, the model was run deterministically and the batch throughput of each run was recorded. Using the base case (0% variability for all parameters) the impact of each parameter change could then be recorded as a % change in batch throughput against the base i.e. against 0%. Figure 17 shows the results of the analysis for all three titers using Tornado diagrams. The biggest impacts are due to the unit operation yields, failure rate and titer. The column height, split ratio limit and resin lifetime, have no impact and the column diameter and DBC only have negative impact. This is due to the fact that at low titers, the number of splits or cycles required through the Protein A column are sufficient enough to handle the variation in titer. Increasing the column dimensions or the split ratio limit will not make a difference to the amount of product able to bind as it is already maximized. Likewise, decreasing the split ratio limit by 20% still allows for the required cycles. Decreasing the column diameter and DBC however raises the required cycles thus resulting in a decrease in the amount of product actually binding. The overall batch throughput is therefore reduced.
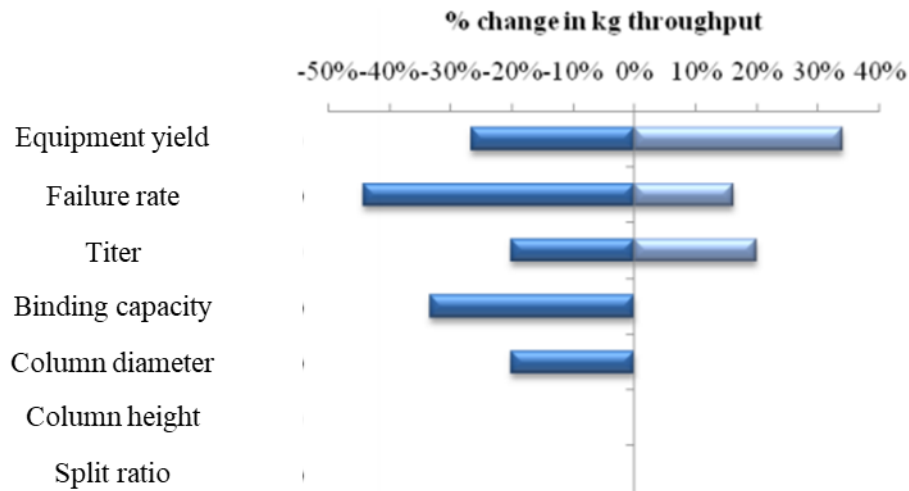
Figure 17: Results from sensitivity analysis

5.4. Results from mathematical optimization tool (VirtECS)

The figure 18 shows the equipment occupancy chart of the process of Product A along with the buffer preparations activities. Alternate grey and white regions represent a period of 1 day. Each batch is represented by the same color coding while the cleaning and steaming activities are in yellow and red respectively. All buffers and their hold vessels are represented with separate colors. Facility downtime is difficult to visualize in the chart but can be validated by checking the start times of activities.

Buffer volumes left in the hold vessels or consumed by each of the activities can be tracked using the resources tracking charts. The figure 19 shows the drop in the buffer volume in the hold vessels as they are consumed by each of the activities as well as the rise in the buffer volumes after refilling activity.
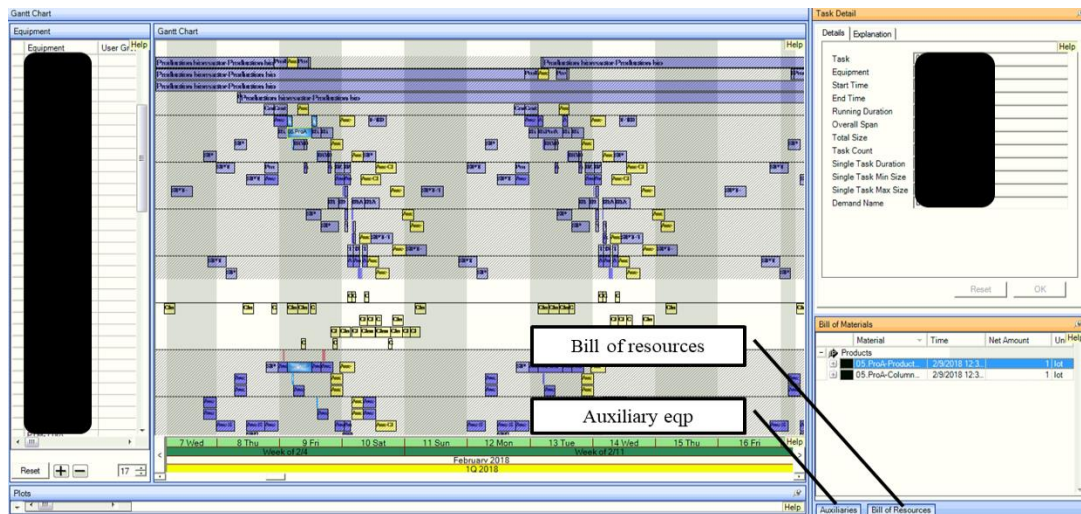
Figure 18: Equipment occupancy chart in VirtECS
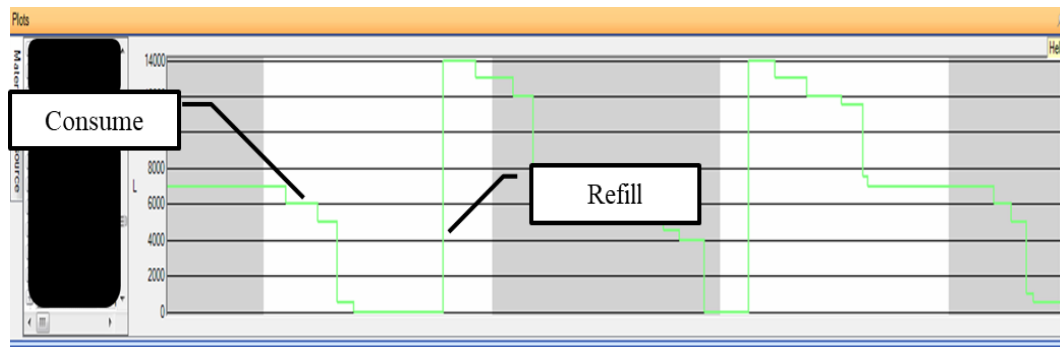
Figure 19: Resources tracking chart in VirtECS

The task detail tab for any given activity can be brought by selecting that activity from the equipment occupancy chart as can be seen in figure 18. Task details tab summarizes all the operating and scheduling information of that given activity. It has a separate sub tab for different types and amount of buffers consumed, second sub tab for the bill of resources needed to start the activity and a third sub tab for the list of auxiliary equipment that are used by the activity. This feature prevents the user from switching back and forth between the model recipe and equipment occupancy chart and saves a significant amount of time.

Operation flexibility: In the case of stochastic delays certain activities need to be started later than their scheduled start time. Such delays may result in conflicts due to buffer, auxiliary equipment, utilities, facility downtime etc. In such a case the user can resolve conflicts either by sliding the activity to happen at the desired time or by forcing the activity to happen at that time. Sliding activities involve delaying the activities within a certain limit, provided all resources and constraints are met, such that none of the other activities need to be delayed. The software specifies this sliding limit for all the activities. This feature is very helpful for the user to know the maximum limits of each of the activities such that other scheduled activities are not disturbed. Forcing delay in activities results in disturbing other scheduled activities as well. This results in changing a larger part of the schedule especially when the schedule generated is too complicated. But the software handles this type of delaying efficiently and rearranges subsequent activities accordingly.

5.5. Result analysis of recipe based scheduling model (SchedulePro)

For consistency, all scenarios are based on a campaign of 13 batches of the same productA.

5.5.1. Process bottleneck:

The cycle time of the process (takt time) was fixed to 5 Days instead of a fractional value so as to have consistency in the upstream and downstream process for all batches. The software indicated the bottleneck equipment as the seed bioreactor with a minimum cycle

time of 4.44 Days. This bottleneck is also the equipment with the least idle time between successive batches.

Taking a closer look at the schedule of all batches proved otherwise. The software considers material transfer as soft constraints i.e. they are not strictly followed but are reported if there is any violation. Since there were no violations reported by the software and also none seen from the material tracking charts it is concluded that all material transfer were completed in the 5 day cycle time of the process. Practically, the next batch cannot start unless all material transfers for it to run are completed. For eg operations cannot run if adequate buffer is not present in the buffer hold vessel and have to be delayed. Figure 20 maps the operation which empties the buffer hold vessel and the operation of the next batch which needs the same buffer. The buffer hold vessel has to be CIP'd and SIP'd before it is refilled. Therefore, the next batch can only be started after this transfer is completed. The transfer is delayed due to Transfer Panel-2 (name changed) which leads to a cycle time of 4.5 days. Since this cycle time is greater that the cycle time of the seed bioreactor the real bottleneck equipment becomes Transfer panel-2. The reason the software did not point to Transfer Panel-2 is, perhaps, because

- It does not reach 100% utilization and therefore does not have the least idle time which is the governing criteria for determining the bottleneck equipment.
- Material transfer is considered as a soft constraint by the software. Hence successive batches will not be delayed if there is a delay in material transfer.
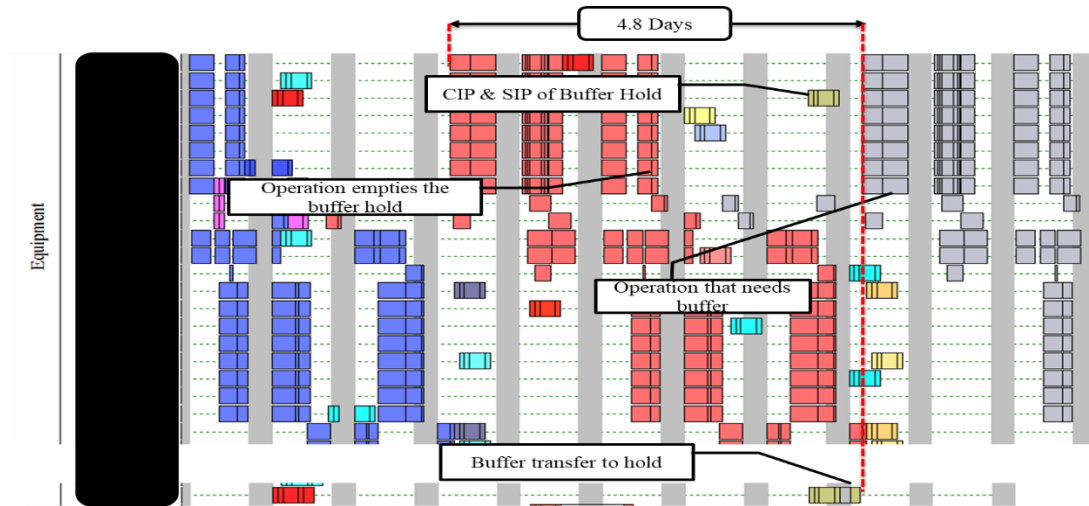
Figure 20: Equipment occupancy chart of TP

All the 13 scheduled batches have different combinations of buffer preparations which

leads to the bottleneck equipment that may differ every batch. Table 4 summarizes the

upstream and downstream cycle time of all the batches. Thus the minimum cycle time of

the process (takt time) will be the maximum cycle time of upstream or downstream

process.

Batch	1	2	3	4	5	6	7	8	9	10	11	12	13
DNS cycle time (Days)	-	5.2	4.7	5.2	4.7	5.5	4.7	5.2	4.7	5.2	4.7	5.2	5.7
UP cycle time (Days)	-	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4

Table 4: Cycle time of different batches

Even if batch 5 has the highest number of preparations and transfers, according to the

table 4, may not be considered as the worst possible batch. As a matter of fact batch 13

has a higher cycle time than batch 5. Buffer preparations of batch 5 are spread across

different days of the schedule but in case of batch 13 there are preparations scheduled for

the same day and uses the same transfer panel, therefore resulting in increased cycle time.

5.5.2. Debottlenecking:

The conspicuous bottleneck equipment common to most of the batches will be the seed

bioreactor with a cycle time of 5.4 days. Followed by the production bioreactor with a

cycle time of 5.3 days is the next bottleneck equipment, in the upstream process. Both of

these reactors have very high utilization time and very low idle times. Hence, the only

way to debottleneck them is by incorporating additional reactors in staggered mode. This

reduces the upstream cycle time significantly (to below 5 days) but at the cost of very

high investment. Also, this investment will not be justifiable if the downstream is not able

to cope with the new cycle time of the upstream process as can be seen from the table 4.

Ways to debottleneck the downstream process by adding new equipment/transfer panels

were proposed which resulted in significant changes in the instrumentations and piping of

the facility and therefore were dropped. The maximum reduction in the cycle time of the

downstream process by only rearranging operations or using equipment already in place

is to 5.1 days. Thus the cycle time of the process (takt time), which should be a whole

number still remains as 6 days. Hence new investment in the bio-reactors become

illogical.

5.5.3. Flexibility analysis:

The cycle time of the process (takt time) cannot be brought down but the schedule can be

made more flexible. If the operations are scheduled very close to one another then delay

caused in any of the operation, which is common in a batch facility, will also delay other

subsequent operations. But if operations are scheduled sufficiently apart, so as not to delay subsequent batches, then chances of propagating the delay reduces and hence the schedule can absorb delays making it flexible. Several ways were proposed

Operations started during the facility downtime: the reason operations cannot be started during the downtime is because there aren't enough trained personnel. But these operations once started can go to completion without having to be monitored. Additionally, CIP and SIP operations are the reason behind many delays caused in the facility. Thus, adding extra labor to specifically start CIP and SIP during this downtime period provides a larger window where these operations can be scheduled. Therefore there will be fewer chances of delays being propagated.

To justify this, the highest used CIP skid in the facility was chosen to experiment on. All the CIP operations of equipment which use this skid were delayed by a certain amount and its effect on the cycle time of the process was seen. The initial model where the CIP and SIP can only be started during the operational time absorbed delays of 0.5 hrs. before the cycle time of the process exceeded 6 days. While the model where CIP and SIP can be started during the facility downtime absorbed delays up to 2.5 hrs. before the cycle time of the process exceeded 6 days.

Consecutive unit operations completed on the same day: currently every unit operation is done on a new day. If a unit operations revolving around the downstream bottleneck equipment is done one day prior as shown in figure 21 then buffer hold vessels can be released earlier. These hold vessels can then be cleaned and refilled therefore giving room to absorb any delays caused.
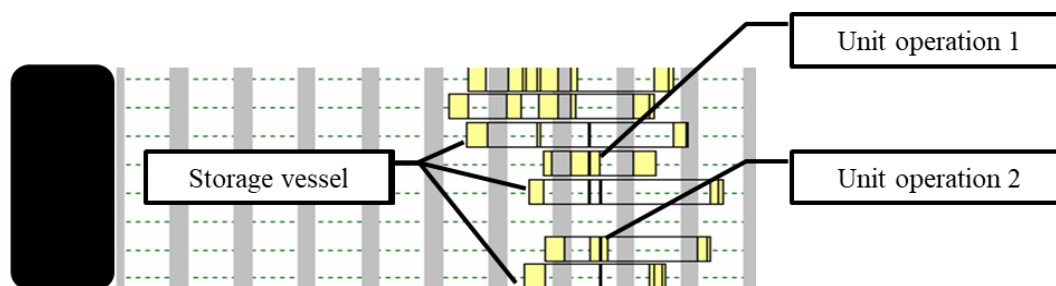
Figure 21: Equipment occupancy chart of the DNS process

Adjusting the sequence of operations: the sequence of operations in any of the downstream unit operation is as follows- equipment SIP then the equipment is washed using buffers (pre-use wash) then operations which act on the drug substance (process activities) then the drug substance is transferred out followed by additional buffer flushes (post-use wash) and finally the CIP operation. All these operations cannot happen during the operational time of a single day and therefore are divided across days. Presently pre-use wash and process operations are done on the same day while the post-use operations are done on the next day. Then the buffer hold vessels are released for their cleaning and refilling which also use the same auxiliary equipment as the unit operations-1 done 2 days earlier. If there is any delay in the release of the hold vessel after post use wash then it might delay the unit operation -1 of the next batch. Therefore if the pre-use wash is done the night before the start of process activity then the post use wash can be completed on the same day thereby releasing the buffer hold vessels earlier and providing more room for absorbing delays.

Alternate buffer hold vessel: different buffer hold vessel with already established piping and instrumentations can be used to store buffer. This may reduce the load on the transfer panel used to transfer buffer from the preparations vessel to hold vessel and also add flexibility. The tables 5 and 6 shows the transfer panels used by different hold vessels

with their filling frequencies and the unit operations after which they are released. If the

buffer hold vessel B-105 is used instead of B-101 then the two filling operations of buffer

will use the transfer panel TP-1 instead of TP-2. This may not decrease the load on the

transfer panel as can be seen from the filling frequency but can add flexibility since the

release dates are significantly apart.

TP-2	Filling frequency	Released after
B-101	1	ProA
B-101	1	
B-102	2	TFFf
B-103	4	ProA
B-104	3	ProA

Table 5: TP-2 being used by different buffers

TP-1	Filling frequency	Released after
B-105	Not used	Not used
B-106	4	AEX
B-107	4	AEX
B-108	2	TFFi

Table 6: TP-1 being used by different buffers

5.6. Result analysis of mathematical optimization model (VirtECS)

The decision variables, objective function, and constraints that are associated with an

optimization problem are defined by the software itself. Since Advanced Process

Combinatorics keeps most of the information proprietary and therefore a complete

analysis on how the optimization is carried forward or what exactly the objective function

is cannot be obtained. This section discusses the results based on only comparison of the

schedules generated from SchedulePro and VirtECS Scheduler. This comparison is used

to propose the working of VirtECS Scheduler and evaluate its capability to produce an

optimal sequence of activities.

The following differences were noted -

- In SchedulePro the buffer hold vessels are refilled as-soon-as-possible. That is once the buffer hold vessel is released for its CIP and SIP it is refilled irrespective of when the buffer is needed in the next batch. Several buffer hold vessels can be released for refilling at the same time. However, the sequence of their refilling operations depends on the date of release of hold vessels, the availability of auxiliary equipment, CHT, DHT, and SHT.

  In VirtECS, the same logic is followed for refilling the buffer hold vessels with the same set of constraints determining the filling sequence.

- TFF-2 releases two tanks for cleaning after it has completed processing, at the same time namely TF-1 and TF-2. Both tanks use the same CIP skid and take the same time to be cleaned but they use the different auxiliary equipment. TF-1 uses an auxiliary equipment TP while TF-2 does not use any auxiliary equipment.
  In SchedulePro the sequence of the CIP of TF-1 and TF-2 need to be specified before generated the schedule in order to prevent any conflicts. While in VirtECS, the software schedules the CIP of TF-1 prior to the CIP of TF-2 simply so that the auxiliary equipment TP becomes available early.

- In SchedulePro the product operation is started as soon as the product operation of the previous unit operation is completed. While the preparation operation is completed before the start and cleaning operation is immediately started after the end of product operation. These operations are scheduled as per the scheduling sequence without any delays. Delay can only be incorporated if flexible shift or a fixed time shift for these

operations is explicitly specified. For eg whether a TP should be occupied during the buffer hold vessels CIP first or downstream vessel first should be specified.

In VirtECS, only the product activities are linked to one another while the cleaning and preparation activities are linked to the product activity. Among them the activities that are to be strictly followed by one another, the sequence is provided for eg cleaning activity is to be strictly followed by product activity. Then there are activities whose sequence is unimportant as long as they are completed. For eg cleaning activity can be comprised of two CIP activities the sequence of which does not matter as long as both of the CIPs are completed. For such activities, VirtECS decides the sequence based on the objective function. It is also observed that irrespective of the sequence, the cleaning activities are started as soon as possible whereas the preparation activities are finished just in time.

From the above examples, it can be concluded that the objective function of VirtECS is minimizing the cycle time of each equipment subjected to various hard and soft constraints. That is minimizing the idle time between all the activities that occupy an equipment for each batch. It minimized the time gap between activities of buffer hold vessels by refiling them as soon as possible in eg 1. It minimized the idle time between activities that occupy the auxiliary equipment TP in eg 2. It also minimized the gap between the preparation, product and cleaning activities and is capable of reshuffling activities to decide the best possible sequence as can be seen in eg 3.

Hard constraints that were observed are equipment/auxiliary equipment, resources, mass balance, scheduling sequence. Also, the soft constraints observed were maximum hold times, clean hold times, dirty hold time, target prep ahead.

Does the optimization of this objective function lead to an optimal sequence of activities? Case 1 supports the proposed hypothesis while case 2 contradicts it.

Case 1: Figure 22 shows the equipment occupancy chart of PTMs from SchedulePro and VirtECS Scheduler respectively. In SchedulePro the CIP operations of tanks used for TFF-2 is immediately scheduled after the TFF-2 product operation is completed which would seem intuitive. After the TFF-2 tanks are CIP'd the buffer hold vessels used during TFF-2 operations undergo CIP followed by SIP and then refilled. The CIP and SIP of the buffer hold vessel occupy two different PTMs. PTM 1 is used for AEX whereas PTM-2 is used for TFF-2 as can be seen in figure 22. The actual TFF-2 tanks are not occupied during the buffer hold vessel operations.

On the contrary, the equipment occupancy chart from VirtECS has the CIP of the TFF-2 tanks delayed within the limits of the tanks dirty hold time. This intentional delay is sufficient enough so as to accommodate the CIP and SIP of the buffer hold vessels as can be seen from the figure 23. This results in PTM-1 to have less idle time as compared to the PTM-1 from the schedule generated in SchedulePro. Note that rearranging activities of PTM-2 does not have any effect on its occupancy time. But since the TFF-2 tanks are not occupied during the buffer hold vessels cleaning activities, delaying their CIP increases the idle time of these tanks which works against the objective function. Hence it is seen that despite the objective function of minimizing the idle time the software can prioritize the equipment to reduce the idle time of by compromising the idle time of certain other equipment and therefore leading to an optimal sequence of events. In this case, PTM-1 (whose cycle time is reduced) should be available in time for AEX of the next batch whereas TFF-2 tank (whose cycle time is increased) is used much later for the

next batch. Also, if it is decided to follow the sequence as per SchedulePro, any delays in the CIP of TFF-2 tank will result in a delay of the subsequent batches until PTM-1 becomes available or the buffer hold vessel is completely filled.

Hence it could be said that the software gives an optimal path for the production recipe of product A.
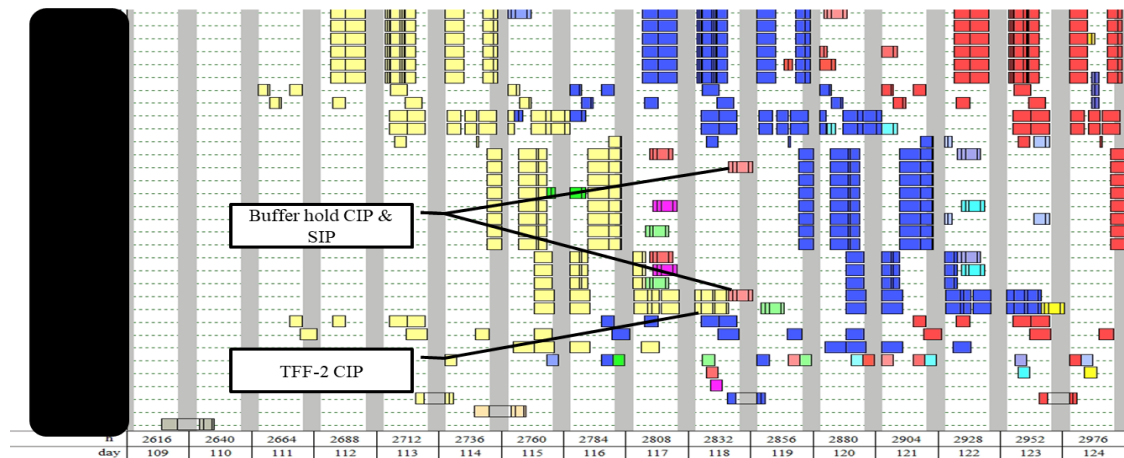
Figure 22: Equipment occupancy chart of PTM in SchedulePro
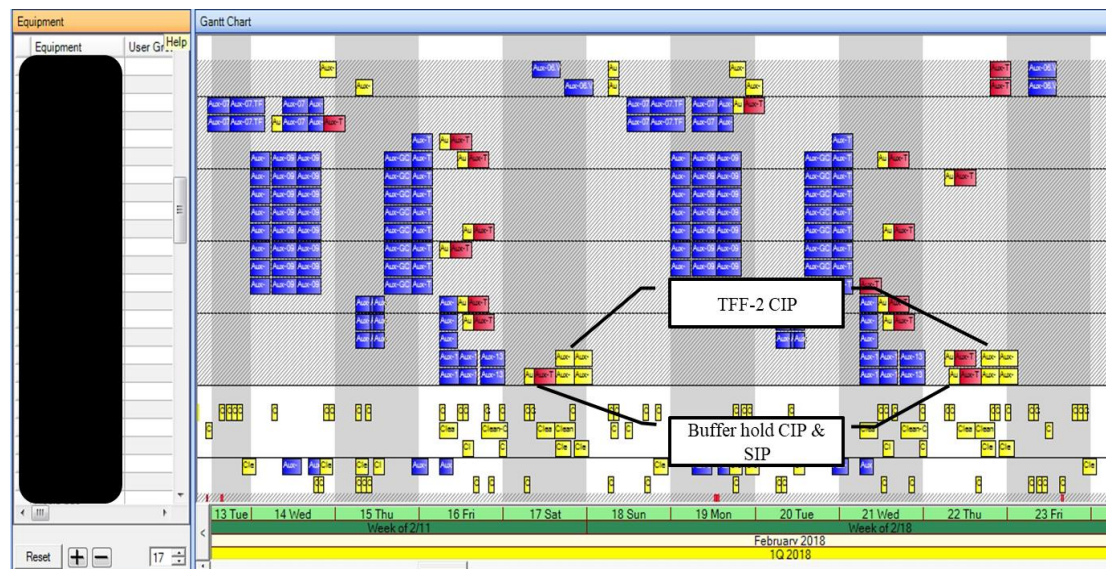
Figure 23: Equipment occupancy chart of PTM in VirtECS

Case 2: considers three buffers, namely B-10, B-11, and B-12. B-10 is used by AEX

column operations and its CIP, B-11 is used by AEX column operations and B-12 is used

by VI and AEX column operations. They all are refilled every batch and use the same

preparation vessel. The preparation vessel has to be CIP'd before a new buffer is made

up. Specific buffer hold vessels are used for each buffers which are also CIP'd before

transferring the new made-up buffer. These hold vessels are refilled as soon as possible.

The buffer preparation sequence in the preparation vessel is as follows B-12, B-11 and B-

10 which is decided by the software. Since AEX unit operation is followed by VI unit

operation B-12 is scheduled to be prepared first. In order to reduce the idle time of the

hold vessel, B-11 is scheduled second since AEX CIP occurs after AEX column

operations. And finally, B-10 is scheduled immediately after B-11 in order to reduce the

idle time of the preparation as well as hold vessel. This can be seen in figure 24
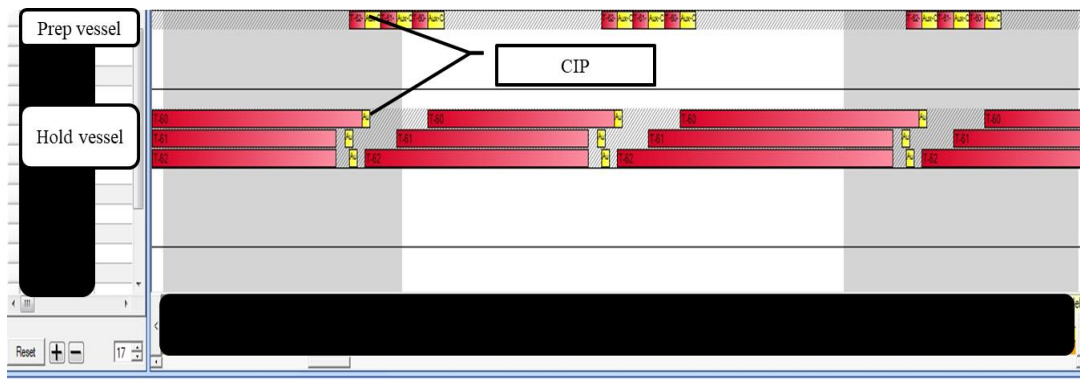
Figure 24: EOC in VirtECS without auxiliary equipment
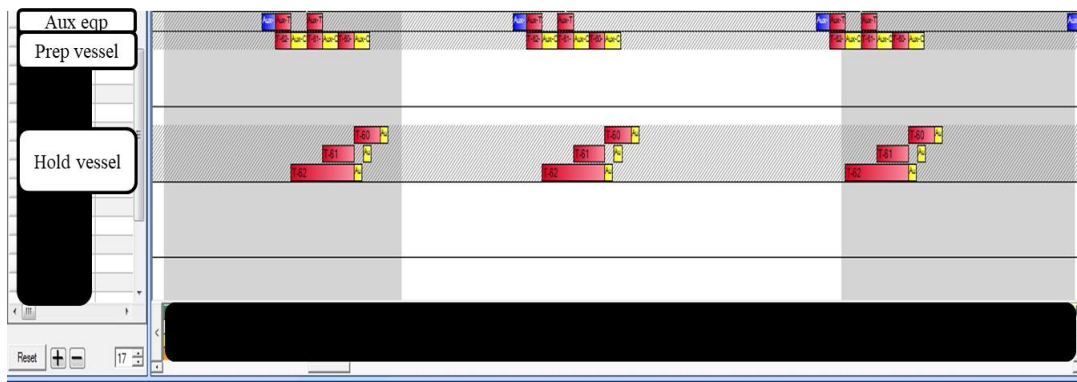
Figure 25: EOC in VirtECS with auxiliary equipment
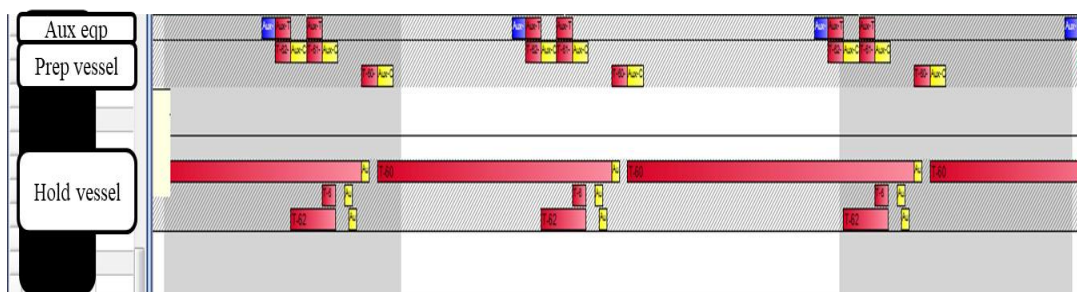
Figure 26: EOC in VirtECS with additional prep vessel

Figure 25 considers an auxiliary equipment which is used by the preparation activity of proA and during buffer preparation of B-11 and B-12. The buffer preparation sequence remains the same but the preparation is started after the cleaning activity of ProA is completed. Thus giving priority to the auxiliary equipment, as against buffer hold vessels, and minimizing its idle time. Figure 26 considers a new preparation vessel for buffer B-10 and it is observed to behave like figure 24 i.e. prepared as soon as possible. The sequence of buffer preparation, in this case, changes to B-10, B-12, and B-13. Thus the sequence of buffer preparation depends on the auxiliary equipment and therefore may not be optimal.

Thus the level of constraints in a given facility will decide if the proposed hypothesis holds true or not. The inability to specify, in the software, the priority of equipment upon

which the objective function should be carried may prevent the software from giving the

optimal sequence for all type of constraints and further the optimal activity start times of

individual activities.

Chapter 6: CONCLUSION

6.1. Project outcomes:

It is shown that a simulation and a scheduling tool can play an important role in biomanufacturing facility. A deterministic study was carried out in order to determine those parameters whose variability would significantly impact the output metric, batch throughput. It showed that at different titers, different parameters had impact, with the protein capture column parameters becoming more significant as the titer increased.

Another study showed that the bottleneck equipment could be different for different batches. The debottlenecking strategies that were proposed requires more detailed cost analysis before their huge investment could be justified. Therefore, currently the process cannot be debottlenecked. But several improvements to the process were proposed to prevent the propagation of delays in the schedule that may significantly delay subsequent batches of the campaign.

Mathematical optimization tools, as opposed to recipe based scheduling tools, are very complicated to work with especially when the level of constraints that need to be modeled are very high. Since most of these type of software does not release information due to proprietary issues, it isn't easy to work on without knowing what is at their core. The user who reads the outcomes may not be able to comprehend its source and leading to manual interventions and thus compromising the results.

Finally, this project can be viewed as a roadmap for implementing a new platform for various day-to-day activities in the industry. Traditional excel based interface lack capabilities and is very time consuming to work on because of lack of dynamic nature. These softwares which are designed for this specific industry offer wide variety of

capabilities. They can address real-time issues, increase operational efficiency as well as save valuable time for employees.

6.2. Software limitations

6.2.1. SuperPro Designer

- It is a simulation software, therefore, lacks the basic capabilities of a scheduling tool. A simulation software requires a well-defined production recipe and cannot have conditional constraints like equipment pool. Therefore equipment assignment has to be done manually before allocating equipment to different procedures.

- Every batch scheduled is identical which is repeated after a fixed cycle time to form a campaign. In such as case scheduling specific buffer preparations, which do not happen every batch, becomes difficult. It also prevents the use of different vessels for different batches since different vessels use a different set of auxiliary equipment.

- Facility downtime cannot be incorporated because the operations are relative to one another that is they are scheduled as soon as the reference operation is completed or completed before the reference operation. They cannot be relative to a certain date or time of the year. Since facility downtime happens every day for a specific time it becomes difficult/impossible to relate the two.

6.2.2. SchedulePro

- Conflict resolution considers facility outages, equipment staff as hard constraints while materials, labor, and utilities as soft constraints. It means that the schedule generated will strictly follow hard constraints but may or may not follow the soft constraints. Practically it is not possible to start unit operations without filling the

buffer hold vessels which the software may decide to ignore. Therefore these soft constraints have to be manually checked for any violations.

- It is a finite capacity scheduling software i.e it delays operations, within flexible limits, if they compete for unique resources. It does not optimize the schedule and determines the best sequence of events. Thus the operation to be delayed has to be specified. Thus optimal schedule can be achieved through scenario testing. However partial optimization of start and finish times is possible (minimize the cycle time of process)

- The model should be separated into upstream and downstream while looking at the time utilization charts. Even though the cycle time of the process is few days the batch time is in months. It takes months after the start of upstream to start the downstream of the first batch. Therefore time horizons for upstream and downstream will be different while looking at the time utilization charts.

- The model can be run in both deterministic as well as probabilistic ways. Both ways may never reflect the actual batch in the facility if data is not accurate. Therefore any minor change in the facility should immediately be incorporated in the model.

6.2.3. VirtECS Scheduler

- There are multiple soft constraints like clean hold times, dirty hold times, maximum hold times. Even though they are considered as soft constraints by the software they cannot be violated in the actual manufacturing environment. Violation of these constraints results in penalties that consume additional resources and may occupy equipment. In order to have a complete optimization, these constraints are equally important.

- The schedule is generated with the objective function of minimizing the idle time. The activity is scheduled by the software which already knows its duration. But during actual manufacturing that activity may take longer than the specified time. If a longer duration is specified and a new schedule is generated then the software may schedule that activity with an earlier start time so as not to alter any subsequent activities. It would have been too late already on the manufacturing scale to start the activity early.

- Minimize idles time, therefore, SIP operations are considered part of the previous batch and therefore scheduled way in advance. Due to several automation and equipment manifold constraints, the SIP of an equipment needs to be started way in advance. Sometimes the software considers the SIP activity as part of the previous batch and schedules it as soon as the last activity of that equipment in the previous batch is completed rather than the intended start time.

PRESENTATION RECORD

Paper:

Title: A comparison between batch and continuous monoclonal antibody production and economic analysis

Author: Ou Yang, Siddharth Prabhu, Marianthi Ierapetritou

Manuscript in preparation

Presentation:

- **Title:** Software evaluation

Author: Siddharth Prabhu, Marianthi Ierapetritou

Summary: Brief overview of the capabilities of software packages and how they align to attain the project objectives

Date: July, 2017, Eli Lilly, Indianapolis

- **Title**: Capacity modeling results

Author: Siddharth Prabhu, Marianthi Ierapetritou

Summary: Discussion of preliminary results on capacity analysis, materials consumed, waste generated and equipment design parameters

Date: October, 2017, Eli Lilly, Indianapolis

- **Title:** Excel integration

Author: Siddharth Prabhu, Marianthi Ierapetritou

Summary: Using excel for transferring data and preliminary results on sensitivity analysis

Date: November, 2017, Eli Lilly, Indianapolis

- **Title:** Buffer preparation

Author: Siddharth Prabhu, Marianthi Ierapetritou

Summary: Reviewing that the buffer preparation sequence as well as the logic and constraints in the facility are accounted for

Date: January, 2018, Eli Lilly, Indianapolis

- **Title:** Scheduling software packages

Author: Siddharth Prabhu, Marianthi Ierapetritou

Summary: Comparing SchedulePro and VirtECS scheduler as potential scheduling software for accounting any complex constraints

Date: February, 2018, Eli Lilly, Indianapolis

- **Title:** Estimating takt time and debottlenecking

Author: Siddharth Prabhu, Marianthi Ierapetritou

Summary: Discussing the root causes for current takt times and the equipment responsible for the same

Date: June, 2018, Eli Lilly, Indianapolis

- **Title:** Revised results

Author: Siddharth Prabhu, Marianthi Ierapetritou

Summary: Discussing the results on takt times and bottleneck equipment due to improved scheduling logics and additional constraints from the last model. Sensitivity, capacity and flexibility analysis was also put

Date: July, 2018, Eli Lilly, Indianapolis

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APPENDIX A – SAMPLE SUPERPRO MODEL
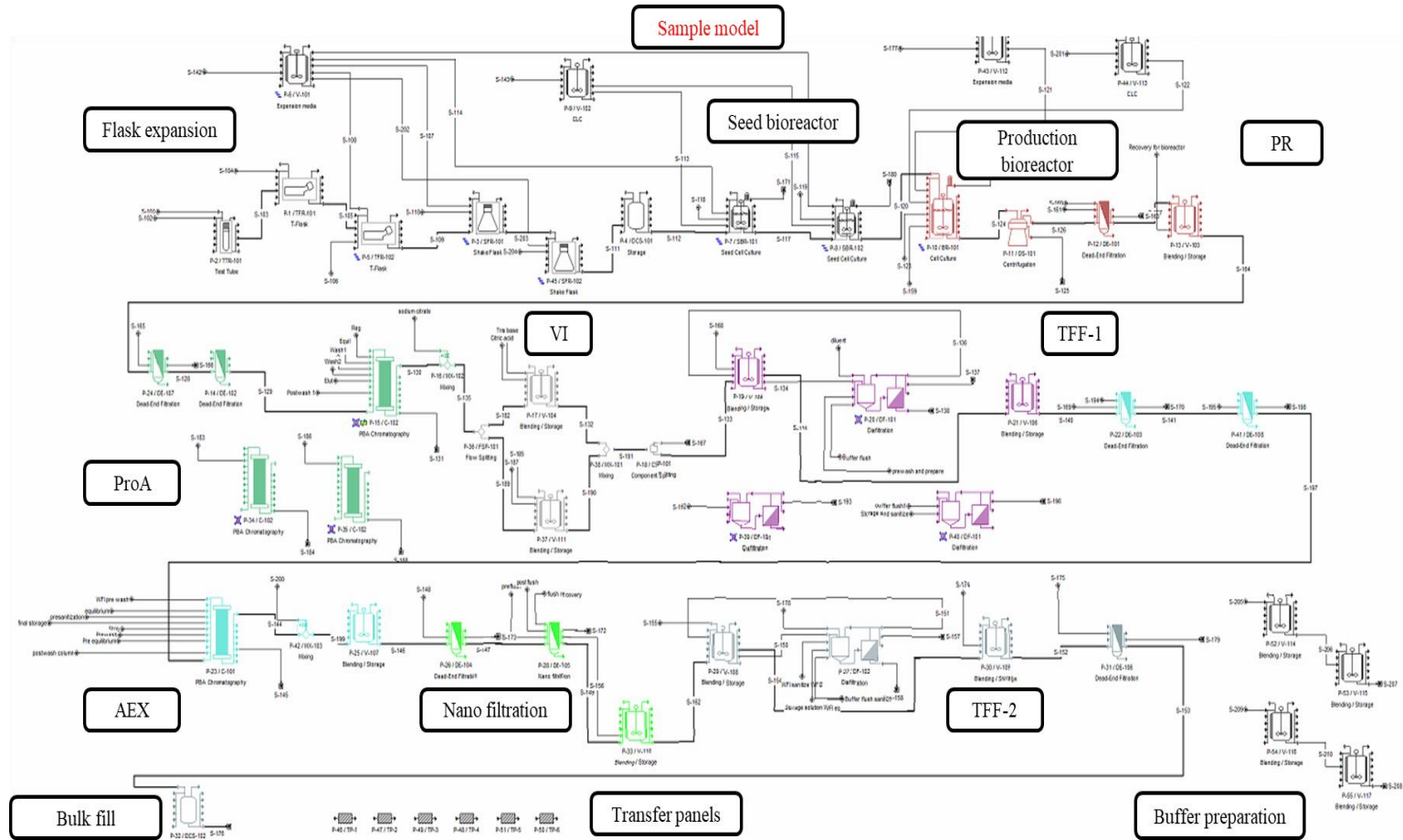
APPENDIX B – BUFFER PREPARATION

Setup: there are 18 buffer hold vessels which are used to transfer buffers to various unit operations. Each hold vessel has a filling frequency between 1 to 4 batches per prep (assuming that they are not filled between two different unit operations of the same batch). Thus, in a set of 12 batches all different combination of buffer preparations is accounted for (LCM of 1,2,3,4 is 12). There are five buffer preparation vessels which are used to prepare buffer depending on their availability. Buffer vessel has to be drained, CIP'd and SIPd before refilling. The expiry time of buffers is very large compared to the time between two refilling (hold times of buffers). Buffer, if required by a certain unit operation, is filled before the start of the first task of that unit operation even if it is actually required by the last task of that unit operation.

Preparation schedule: Consider for e.g. six buffer hold vessels (101 to 106) with their filling frequency and starting volumes as shown in the table 7. If the starting volume of buffers in hold vessels is 0% of its working volume then all buffers have to be prepared before batch 1, 13 and so on. Thus, there will be an uneven distribution of buffer preparation across the 12 batches as shown in the table 7. This may significantly affect the takt time if there are a large number of hold vessels. But if the starting volume of buffer hold vessels is adjusted as shown in the table 8 then the buffer preparations are evenly divided across the batches as can be seen in the table

Buffer	Filling frequency (Batch/prep)	Starting volume (%)	1	2	3	4	5	6	7	8	9	10	11	12	13
101	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
102	2	0	1		1		1		1		1		1		1
103	3	0	1			1			1			1			1
104	4	0	1				1				1				1
105	2	0	1		1		1		1		1		1		1
106	4	0	1				1				1				1
		Total Prep	6	1	3	2	5	1	4	1	5	2	3	1	6

Table 7: Buffer preparation with 0% as their starting volume

In the facility this process is not followed from the first batch itself, but rather subsequent batches because the first batch has more cleaning and setup operations than the following batches in a campaign.

Buffer	Filling frequency (Batch/prep)	Starting volume (%)	1	2	3	4	5	6	7	8	9	10	11	12	13
101	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
102	2	0	1		1		1		1		1		1		1
103	3	33		1			1			1			1		
104	4	0	1				1				1				1
105	2	50		1		1		1		1		1		1	
106	4	50			1				1				1		
		Total Prep	3	3	3	2	4	2	3	3	3	2	4	2	3

Table 8: Buffer preparation with different starting volume

Modeling in SuperPro Designer: Certain limitations of the software allows to model only one batch from the set of 12 batches. This particular batch is then repeated several times to form a campaign. Thus, from this set of 12 batches the worst possible batch is chosen to be modeled. This batch is chosen based on the number of CIPs, SIPs of buffer hold vessels (with same/different transfer panels as part of the CIP/SIP circuit) and the number of buffer preparations. It is safe to assume that takt time of this batch will be greater than or equal to the takt time of all other batches.

The preparation vessels have to be manually assigned to each of the six buffer since SuperPro Designer by itself cannot choose from a set of vessels depending on their availability. The vessels are assigned such that the difference between the numbers of batches per prep for each preparation vessel is constant.

Buffer	101	102	103	104	105	106	Total
Filling	1	2	3	4	2	4	
Starting (%)	0	0	33	0	50	50	Total
1	P-101	P-102		P-103			3
2	P-101		P-103		P-102		3
3	P-101	P-102				P-103	3
4	P-101				P-102		2
5	P-101	P-102	P-103	P-103			4
6	P-101				P-102		2
7	P-101	P-102				P-103	3
8	P-101		P-103		P-102		3
9	P-101	P-102		P-103			3
10	P-101				P-102		2
11	P-101	P-102	P-103			P-103	4
12	P-101				P-102		2
13	P-101	P-102		P-103			3

Prep vessel	Batches/prep	Buffers		
P-101	1	101		
P-102	1	102	105	
P-103	0.83	103	104	106

Table 9: Method of assigning preparation vessels

APPENDIX C – SOFTWARE EVALUATION

- Excel Spreadsheet/ Excel solver

Current excel spreadsheets are used for modeling and day-to-day scheduling. Equipment occupancy charts are made in excel. Excel solver is used for what-if analysis.

Pros
- Easy to use. No additional training required
- Easy to link to other systems

Cons
- No connectivity between equipment in the schedule
- Lot of time and effort required to build them

- RTMS, Cross walk (Bio-G)

A discrete event simulator works on Resource Task Network (RTN) concept.

Pros
- Partial optimization can be achieved
- Linking various data sources to provide results on quality by design

Cons
- Rely on third party to make any changes
- Cost

- SuperPro Designer and SchedulePro (Intelligen)

SuperPro is a flowsheet modeling tool while SchedulePro is finite capacity modeling software.

Pros
- Specifically designed for pharmaceutical manufacturing
- Partial optimization can be achieved
- Easy linkage allows wide variety of analysis

Cons
- Learning curve
- Features restricted by the number of available options in the software

- VirtECS Scheduler (APC)

A discrete even simulator which works on State Task Network (STN) concept

Pros
- Complete optimization of objective function
- Learning curve

Cons
- Cost
- Limited capabilities than other counterparts

- Aspen One (Aspen Tech)

Aspen One is very similar to SuperPro Designer

Pros
- Adaptable to Biopharmaceutical industry
- Partial optimization is achieved

Cons
- Cost
- Learning curve