

DESIGN AND SIMULATION OF A NEW BIOMEDICAL PRODUCTION PROCESS

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ABSTRACT

This paper presents the design and analysis of a lean production system for a new biomedical technology product that has the potential to accelerate the screening process for cancer treatments. To navigate the unique constraints of the product's manufacturing process, including the use of time-sensitive biomaterial and several steps with long processing times, simulation is utilized to analyze and compare multiple system designs and production scenarios. The final design includes a robust production schedule, a modular facility layout, and lean production control tools for daily facility operation. All of the proposed designs are compliant with regulations governing the correct handling of human tissue and other biomaterials, and guidelines from the regulatory bodies were explicitly incorporated in key decisions throughout the design and simulation modeling process.

1 INTRODUCTION

Cancer screening, early detection, and personalized medicine are at the forefront of cancer research. According to the World Health Organization (2018), approximately 1 in 6 deaths globally were due to cancer. Furthermore, leukemia is one of the most common forms of childhood cancer. The American Cancer Society (2020) estimates there will be approximately 60,500 new cases of leukemia diagnosed in 2020 with an estimated 23,100 deaths from leukemia. To diagnose and treat cancers such as leukemia, more effective screening and treatment methods are needed.

To address this need, researchers have developed a promising product and procedures that can be used for screening for leukemia and the development of personalized medical treatments for leukemia (Li et al. 2018; Li et al. 2019). Sanatela, a medical solutions company, has developed a product called *Matrix*. The Matrix is a gauze-like, natural 3D biological tissue that is made from Wharton's Jelly, a material in human umbilical cords (Sanatela 2020). At the start of our work, the Matrix was being produced in a research lab setting, and the company wanted to design an efficient manufacturing facility to produce the product.

In this paper, we describe how simulation is utilized to design a biomedical manufacturing system for the Matrix product that takes into account biomedical environmental, production, and product tracking regulations as well as production process times that are highly variable. Due to the unique process constraints for the product, and in order to capitalize on the opportunity to create a Lean process from day one of manufacturing operations, simulation was utilized in order to analyze a multitude of configurations prior to selecting the best design. This paper will outline how simulation aided essential manufacturing process design decisions such as facility layout, material flow, employee utilization and regulation compliance.

2 RELATED WORK

As standards have continued to rise for quality, competitive pricing, and just-in-time delivery for products across every industry, new applications of simulation as a tool for identifying improvement opportunities have been increasingly explored in literature. The concept of a “digital factory,” a simulation model that reflects the planned or actual details of a production system to aid decision-makers in understanding and optimizing their operations, has been used to improve many types of processes (Kuhn 2006).

Applications of “digital factories” within the biopharmaceutical field have been particularly useful, since the manufacturing of biomedical products involves many sources of variability and complex constraints that would be difficult to capture without the use of simulation modeling. Wang et al. (2019) developed a stochastic simulation model to analyze risk throughout a biomanufacturing process; this model can be used in identifying the aspects of the process which pose the greatest threats to throughput and quality and in proposing changes to increasing the stability of the process. Simulation can be used to inform biopharmaceutical production planning and increase robustness to uncertainty, as demonstrated by the mathematical programming approach of Lakhdar and Papageorgiou (2008). In addition to internal sources of variation (eg. fluctuating yield in chemical processes), biomanufacturing processes are affected by external constraints and sources of variability, such as changing government regulations and compliance standards; simulation has been used to model the impact of these compliance requirements on biomedical processes (Leachman et al. 2008; Lim et al. 2004). Other applications of simulation modeling in biomanufacturing include identifying potential issues in facility fit and capacity planning (Stonier et al. 2012) and modeling bottlenecks and support functions to determine the best strategy for process improvement (Kulkarni 2015). The aforementioned applications primarily simulate each production process at a relatively high level and focus on changes to production planning to mitigate uncertainty; some researchers have also taken a more micro approach and used simulation to identify improvements by examining the impact of changes in the details of various material choices and stoichiometric interactions throughout the process (Chhatre et al. 2007).

Biopharmaceutical manufacturers are increasingly interested in implementing Lean principles, such as continuous flow, to gain the dramatic improvements in waste reduction that have been seen in other industries. Another approach that has been used to reduce waste is value stream mapping. Nepal et al. (2011) utilized value stream mapping to identify waste in a current and updated manufacturing process. Value stream mapping allowed redundancies and production delay issues to be identified, reducing the overall production time from 17 to 4.5 days (Nepal et al. 2011). This presents another opportunity for the application of simulation; several simulation tools have been developed to optimize throughput in continuous flow-style biomanufacturing facilities (Stonier et al. 2009; Garcia and Vandiver 2016).

In this work, we combine lean manufacturing principles and simulation in the design of a biomanufacturing facility.

3 BIOMATERIAL PROCESSING AND REGULATIONS

A high-level overview of the processes used to produce the Matrix product are shown in Figure 1. The process starts with with umbilical cords that are received for use in the product. The umbilical cords are dissected to remove a substance referred to as Wharton’s Jelly. The Wharton’s Jelly then goes through process of sterilization, decellularization, homogenization, and lyophilization. After inspection, the Matrix product is cut and packaged. (See Sanatela 2020 for more detailed information about the process.)

In addition to the processes and procedures, applicable U.S. Food and Drug Administration (FDA) regulations as well as American Association of Tissue Banks (AATB) and International Organization for Standardization (ISO) standards for the production of human cell and tissue-based products have been taken into consideration. In particular, the FDA regulation applicable for this product is “Title 21 Part 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products”. Part 1271 contains Subparts A-F; however, this product only requires compliance with Subparts C - Donor Eligibility and D - Current Good Tissue

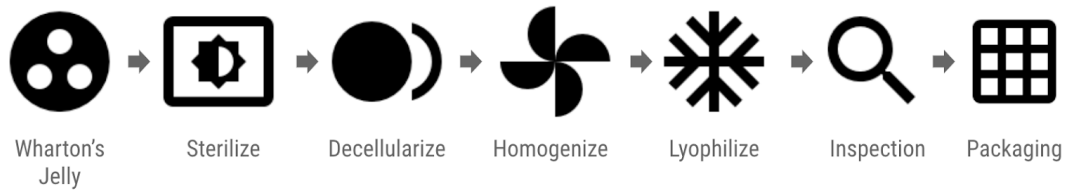


Figure 1: Production process overview.

Practice. Subpart C is applicable to the company, but is not within the scope of this design project. The seven applicable regulations under Subpart D are summarized in Table 1. We will discuss these regulations and their impact on the system design throughout the remainder of the paper.

Table 1: Applicable sections for Human Cells, Tissues, and Cellular and Tissue-Based Products.

CFR	Category	Implementation
§ 1271.170	Personnel	2-5 technicians
§ 1271.190	Facilities	Lab layout, zones
§ 1271.195	Environment Control and Monitoring	Process schedule
§ 1271.200	Equipment	Equipment specifications, process schedule
§ 1271.220	Processing and Process Controls	Process schedule, batching
§ 1271.250	Labeling Controls	Visual control, process control cards
§ 1271.290	Tracking	Process control cards

4 BIOMANUFACTURING SYSTEM DESIGN

In this section, we describe the design process for developing the biomanufacturing system for the product. In particular, we describe the research lab process originally used to produce the Matrix product (current state) and the method applied to design the commercial manufacturing system (future state).

Given a set of standard operating procedures (SOPs) and through interviews with subject matter experts, a current-state value stream map (VSM) of the research lab process was developed (see Figure 2). The VSM highlights the unbalanced nature of the process: each step takes a radically different amount of time, ranging anywhere from a few minutes to several hours. Some information from the original VSM, including steps and duration for each process, has been redacted to protect Sanatela intellectual property.

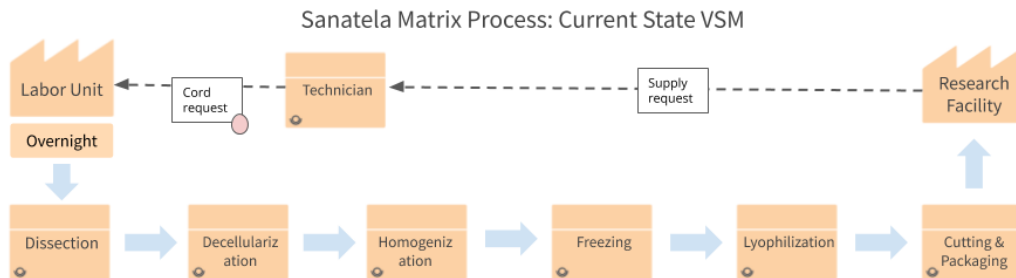


Figure 2: Current state VSM for production process.

A simulation model of the current state was developed. This simulation model gave insights into the dynamic behavior of the system as well as potential ways of translating the research lab process into a manufacturing process. Since the process consists of a sequence of linear steps performed on the same

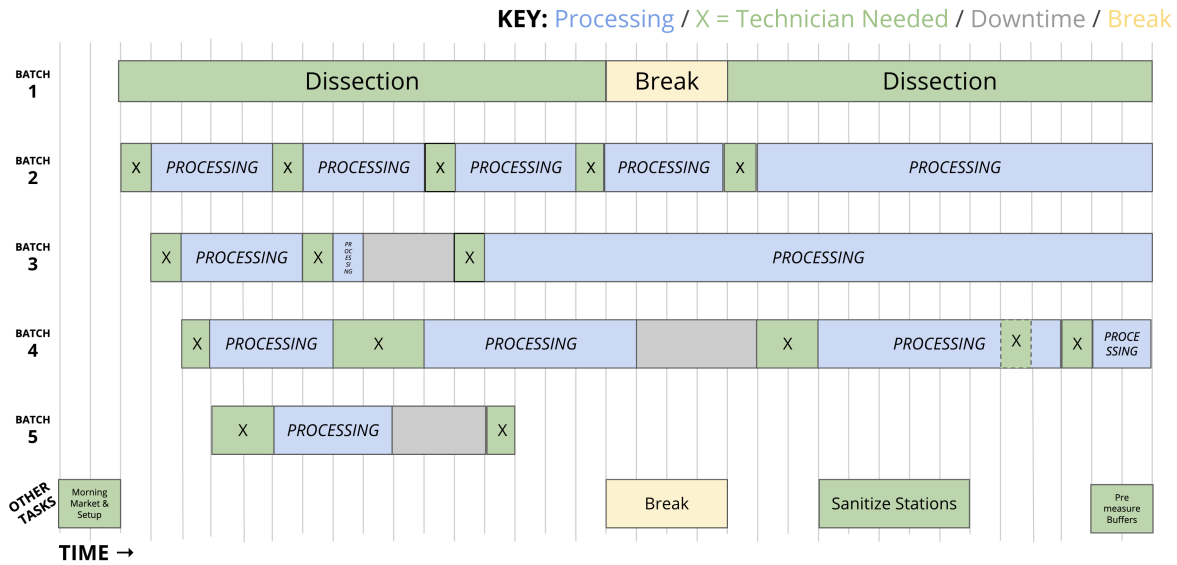


Figure 3: Visual representation of the production schedule design.

input material, there is not much waiting muda (waste) in the current process. However, we determined that processing multiple cords simultaneously could result in of higher throughput as well as balance the workload for the technicians. In particular, we designed a schedule (see Figure 3) for processing the product in which technicians perform two specialized roles with a two-to-one ratio: the first technician role is dedicated entirely to dissection, while the second role (here on referred to as "processing techs") involves completing the same sequence of steps each day in order to process four batches simultaneously. The schedule was created to meet Sanatela's desired takt time while being able to quickly ramp up new labs to a steady state and to meet the company's desired takt time.

The schedule is designed based on the lean principle of Heijunka: the processing technician's work is relatively level throughout the day, with tasks slightly front-loaded to increase the probability that all work will be able to be completed by the end of the day even if issues arise or steps take longer than expected. The processing technician alternates between each batch, completing setup steps with a "waterfall"-esque flow and spending time toward the end of the day on supporting tasks such as sterilizing lab equipment. The process schedule fulfills CFR 1271.170 as it runs efficiently with a flexible number of technicians and accounts for cleaning and sanitation requirements mentioned in multiple CFR sections. This schedule is also ideal for use in a single-piece flow, cellular facility layout.

After receiving additional feedback on the project schedule from company stakeholders, the finalized schedule was used to create a future state value stream map (see Figure 4) and corresponding simulation model. The future state model has the addition of milk-runs for daily supply of umbilical cords from hospitals, lean production control methods, as well as the delivery of products to customers; again, specific process information has been redacted to protect company IP.

5 FACILITY LAYOUT

The biomedical technology company is located in a building with several adjacent "labs" dedicated to production. One of the main priorities of the design was maintaining the ability to easily adjust to company growth and flexibility. Therefore, all lab space was designed with the intention of being modular. The lab space was located between office space and a hallway leading to the shipping and receiving docks. Since the labs require a supply of bio waste, it was very important to simulate the material flow into and out of the lab to mitigate any risk of hazardous waste contact.

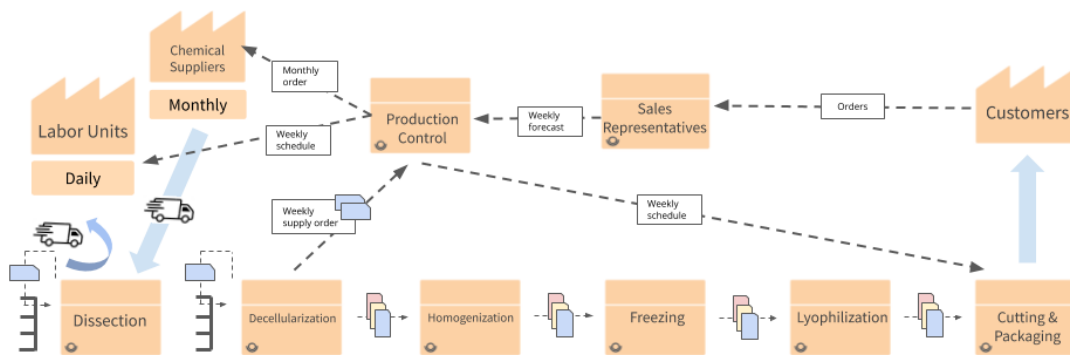


Figure 4: Future state VSM for production process.

As a result of regulation 1271.190, the separation of umbilical cords and extracted Wharton’s Jelly became a priority in the design of the lab space. The proposed solution to this issue is the dual lab set up seen in Figure 5. This design requires a pair of labs: one dedicated to dissecting cords (Zone 1) and one dedicated to the post-processing steps (Zone 2). Separating the labs into two dedicated spaces significantly reduces the probability of cross-contamination. The dissection lab feeds Wharton’s Jelly to the adjacent post-processing labs via transfer windows. A cellular continuous flow product layout is utilized in the design of the lab space. The cell configuration of the lab equipment reduces motion waste of the technician who is required to complete and monitor tasks at multiple stations throughout the shift. This layout also facilitates smooth accommodation of production ramp, since it is modular: as demand increases, Sanatela will be able to expand into additional lab spaces by simply duplicating the two-lab setup. The simulation model was created to demonstrate both the material and people flow between the two labs.

6 SIMULATION AND ANALYSIS

The development of this production process presented a unique and well-suited opportunity for the application of simulation for several reasons:

- Since the large scale manufacturing process had not yet been developed, simulation could be utilized to analyze many concurrent sets of potential options to find an best solution.
- Statistical results from the simulation can provide reasonable estimates for production output and utilization, among other factors. This information will provide information about staffing decisions, production capacity, and lead times, among others.
- The animation features in simulation software can help give stakeholders a more realistic sense of what the physical lab space will look like in its finished state. The simulation’s high-fidelity visual (“digital twin”) will be helpful in thinking through potential problems that could occur with the proposed layout.
- Simulation affords the ability to test less-than-optimal scenarios in order to gather data about the sensitivity/robustness of the system without sacrificing actual lab time or physical materials.

As previously discussed, the first step in capturing and testing data about the production process was creating a current state simulation model. This simulation model is constructed using the Simio simulation software and is fairly straightforward: a source (“Hospital”) generates a new cord for processing every 24 hours, and a technician handles each of the processing steps as the Wharton’s Jelly is transformed before ultimately being packaged. Task sequences in Simio were used to model the complex subtasks included within each higher-level step. In the current state, the technician utilization was determined to be approximately 35%, which is unsurprisingly low given the many steps with long processing times during which no technician is required. Each cord spent a significant amount of time; if this process was simply

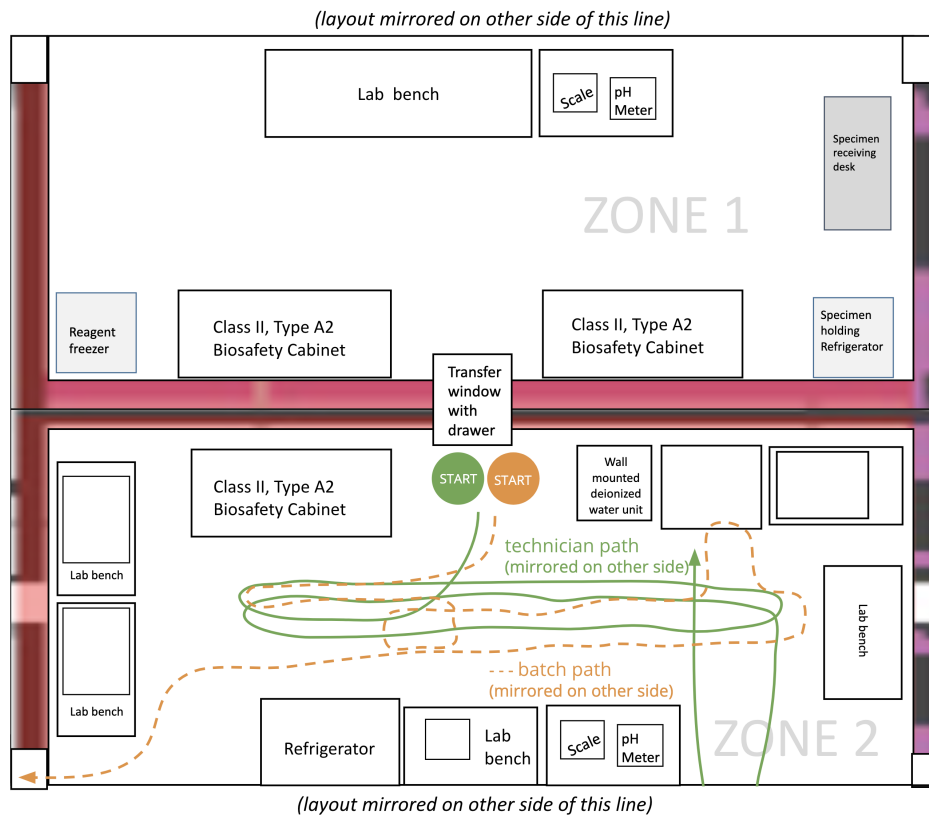


Figure 5: Finalized two-lab layout.

conducted as-is and repeated when each cord was finished, the total weekly output would not meet the desired takt without considerable waste of resources.

A future state simulation model (Figure 6) was created to reflect the new proposed design with two labs. In this model, one lab is dedicated to dissection; the adjacent lab is dedicated to the subsequent tasks handled by the processing technician. Equipment specifications were verified ensuring compliance with CFR 1271.200.

This simulation was used to run several experiments to gather data on the performance of the production process under different scenarios. The following paragraphs will summarize the results from these experiments and specifically address the two most critical metrics (batch output and processing technician utilization).

- Scenario 1 (*Control*): In this scenario, all process times were static and based on the estimates provided in the SOP. This led to very predictable results for each day's output, with 59% utilization for the processing technician.
- Scenario 2 (*Variation* in process times): A triangular distribution for processing times was introduced to model variation in the steps completed by technicians. This led to a 9% reduction in batch output over the same time period and a drop in processing technician utilization due to the additional waiting time when steps were not ready to be addressed when they should have been.
- Scenario 3 (*Optimistic* processing times): The triangular distribution from scenario 2 was modified to create slightly faster processing times on average. Although the processing technician worked more efficiently, because dissection/cord supply is still the bottleneck, the system was unable to produce more batches than in the control scenario.

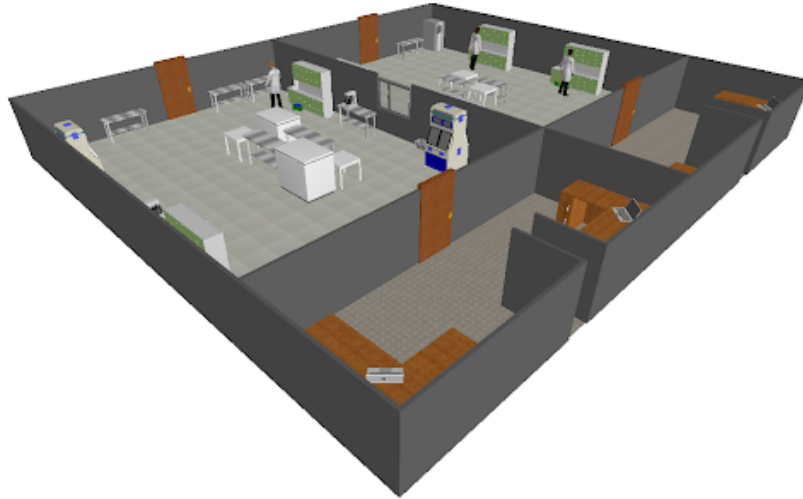


Figure 6: Future state simulation version 2, including two-lab layout.

- Scenario 4 (*Pessimistic* processing times): The same approach was taken to this experiment as in scenario 3; processing technician utilization remained the same but the total batch output dropped by 19% due to the delays.
- Scenario 5 (*Very pessimistic* processing times): This scenario was similar to scenario 4, but more pessimistic - this was conducted to test the effect on the system of having technicians who are still learning/being trained on the process working in the lab, since this will be the case for the company. Completed batches dropped 28%.
- Scenario 6 (*Cord Arrival 1* - variation in cord arrival): Since the number of births and parent consent for cord donation are factors out of the company's control, this scenario was constructed to test the effect on the process of more or fewer cords being supplied to the system than expected. The distribution of processing times was set to triangular ($\pm 10\%$ of the estimated time for each step requiring a technician) to model normal variation in the process. A triangular distribution for cord arrival resulted in 7% fewer completed batches and 4% lower utilization for the processing technician than the control scenario. Scenario 7 (*Cord Arrival 2* - variation in cord arrival): This experiment tested a similar case as scenario 6, but with a discrete distribution for cord arrival - 90% of the time, two cords would be supplied as expected; 10% of the time, only one arrived. Batch output was 4% lower for this scenario.
- Scenario 8 (*Scrap rate*): In this scenario, a 10% scrap rate was included for each high-level step in the process (eg. decellularization, homogenization, etc). This resulted in a 39% reduction of batches being delivered to the customer. Processing technician utilization also dropped to 45%.
- Scenario 9 (*Machine downtime*): This experiment tested the effect of machine downtime on the process output. Each machine in the lab was assigned a processing count-based failure mode with a triangular distribution and one hour of repair time. This resulted in a 3% reduction of batches sent to the customer. Importantly, this scenario did not model the effect of machine downtime on batches waiting to be processed - in some cases, if a machine breaks down for a long enough period of time, the material may expire and need to be scrapped.
- Scenario 10 (*Worst case*): This scenario tested the "Murphy's Law" case for the lab, including reliability issues for machines (scenario 9), a scrap rate throughout the process (scenario 8), inconsistency in cord arrival (scenario 7), and pessimistic processing times (scenario 4). This

resulted in a 55% drop in batch output, 37% of the control number of batches being discarded, and only 40% utilization for the processing technician.

Overall, the results of these experiments (see Figure 7) show that the process is fairly robust to multiple failure modes (longer task times than expected, variation in cord arrival, machine reliability issues, and scrap throughout the process). The difference between the output for the “perfect”/control scenario and worst-case scenario (45% of the control output) seems reasonable. All variation in technician utilization (see Figure 8) is minimal and easily explained by discrepancies such as bottlenecks in the system.

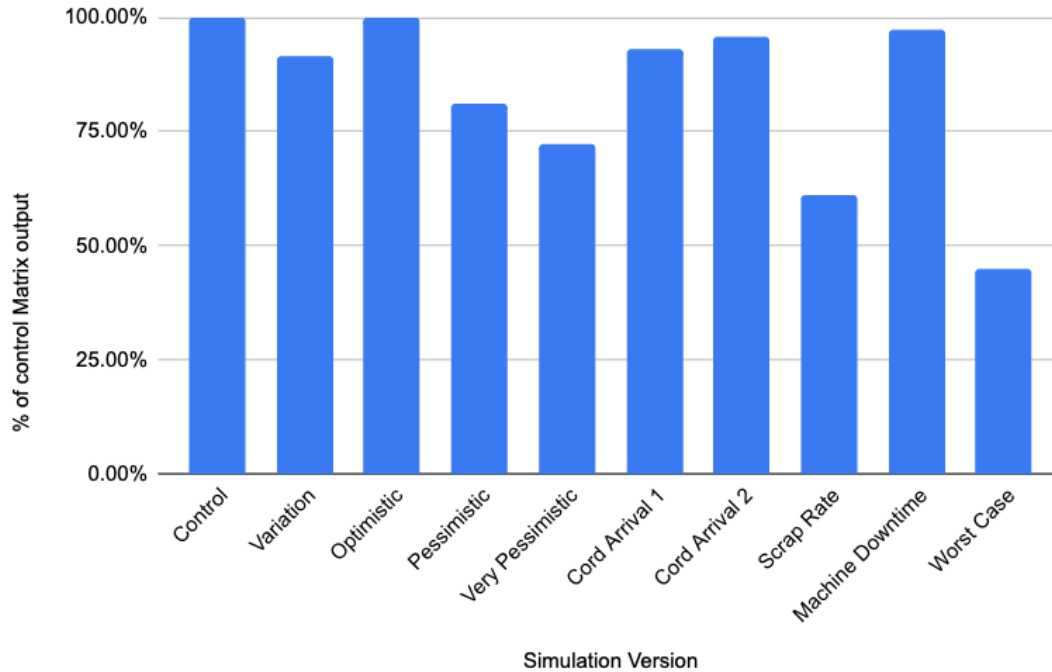


Figure 7: Output of each system simulation.

Based on this data, recommendations to the team include approaching the process slowly and carefully for the first week (or longer) as production begins to ramp up. Since the process schedule is front-loaded, it will not be incredibly difficult to catch up at the end of the day if tasks are running behind, but the consequences of making mistakes and needing to scrap batches as a result of rushing through the steps are high. Because the process requires a week of ramp-up time in order for the line to be wet (a batch in process at every station), there will be ample time for new technicians to practice the process steps without time constraints in order to reduce the probability of mistakes.

7 LEAN PRODUCTION CONTROLS

The opportunity to design this production process from the ground up provided the power to instill a culture of Lean manufacturing in the lab from day one of operations. The proposed solutions, in the spirit of Lean, are all low-cost and simple to implement, understand, and use. They include: daily “morning market” meetings with a problem solving board, poka-yoke/visual controls at each lab station, a kanban-style “batch status” board and Heijunka-inspired schedule board, product tracking cards, and the use of milk runs to level production input. These lean processes were embedded into the simulation model through process times and worker schedules to ensure that there will be ample time for employees to complete all tasks

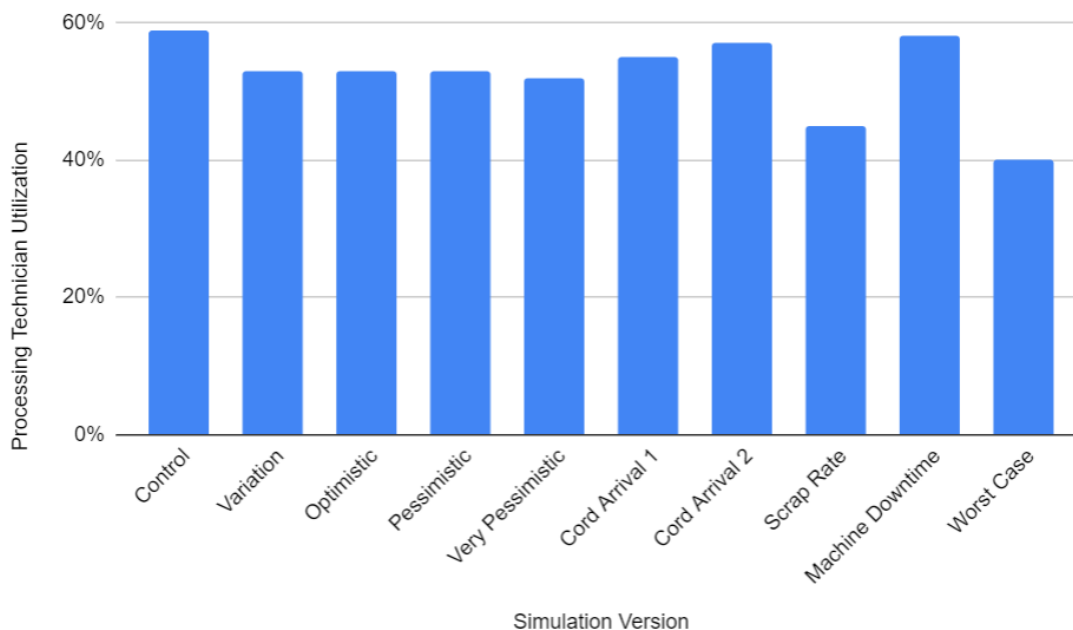


Figure 8: Processing technician utilization for each simulation version.

and continue to run the lab efficiently. These methods conform to CFR 1271.250 and 290 that state that there must be procedures to ensure HCT/P identification and HCT/Ps must be able to be tracked from the donor to the final disposition.

8 CONCLUSION

In this study, we have demonstrated the use of simulation in the design of a biomanufacturing facility for the production of a product that can be used to advance cancer screening and individualized treatments. The proposed process schedule is straightforward and level, and creates high but not ultra-demanding utilization for the processing technician. Standards issued by multiple regulatory bodies have been reviewed and incorporated throughout the lab and process design to ensure compliance and high quality. The lab layout uses space efficiently, incorporates Lean principles for facility design, and minimizes the amount of equipment required to produce the product. A detailed simulation analysis confirms the validity of the process and lab designs, allows testing the impact of many scenarios on production output, and lends a higher-fidelity visual rendering of the future space to generate excitement and trigger proactive problem-solving. Finally, Lean production controls, including visual management devices and triggers for problem-solving, will set the lab on track for continuous improvement as the company continues to evolve.

REFERENCES

- American Association of Tissue Banks (AATB). Standards for Tissue Banking. <https://www.aatb.org/standards>.
- American Cancer Society, Cancer Statistics Center. <https://cancerstatisticscenter.cancer.org/>.
- Chhatre S., R. Francis, K. O'Donovan, N.J. Titchener-Hooker, A.R. Newcombe, and E. Keshavarz-Moore. 2007. "A Decision-Support Model for Evaluating Changes in Biopharmaceutical Manufacturing Processes". *Bioprocess and Biosystems Engineering* 30(1):1–11.
- Garcia, F. and M. Vandiver. 2016. "Throughput Optimization of Continuous Biopharmaceutical Manufacturing Facilities". *PDA Journal of Pharmaceutical Science and Technology* 71(3):189–205.
- International Organization for Standardization (ISO). ISO 14644-1:2015. <https://www.iso.org/cms/render/live/en/sites/isoorg/contents/data/standard/05/33/53394.html>.

- Kuhn, W. 2006. "Digital Factory - Simulation Enhancing the Product and Production Engineering". In *Proceedings of the 2006 Winter Simulation Conference*, edited by L.F. Perrone, F.P. Wieland, J. Liu, B.G. Lawson, D.M. Nicol, and R.M. Fujimoto, 1899–1906. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.
- Kulkarni, N. 2015. "Evaluating Bottlenecks and Support Functions using Simulations in Biotechnology Industry". In *IIE Annual Conference Proceedings*. Norcross, GA: Institute of Industrial Engineers.
- Lakhdar K., and L. Papageorgiou. 2008. "An Iterative Mixed Integer Optimization Approach for Medium Term Planning of Biopharmaceutical Manufacture Under Uncertainty". *Chemical Engineering Research and Design* 86(3):259–267.
- Leachman, R. C., L. Johnston, S. Li, and Z. Shen. 2014. "An Automated Planning Engine for Biopharmaceutical Production". *European Journal of Operational Research* 238(1):327–338.
- Li, D., G. Chiu, B. Lipe, R.A. Hopkins, J. Lillis, J.M. Ashton, S. Paul, O.S. Aljitali. 2019. "Decellularized Wharton Jelly Matrix: a Biomimetic Scaffold for Ex Vivo Hematopoietic Stem Cell Culture." *Blood Advances*. 3(7):1011–1026.
- Li, D., T.L. Lin, B. Lipe, R.A. Hopkins, H. Shinogle, O.S. Aljitali. 2018. "A Novel Extracellular Matrix-based Leukemia Model Supports Leukemia Cells with Stem Cell-like Characteristics." *Leukemia Research* 72:105–112.
- Lim, A. C., Y. Zhou, J. Washbrook, N. J. Titchener-Hooker, and S. Farid. 2004. "A Decisional-Support Tool to Model the Impact of Regulatory Compliance Activities in the Biomanufacturing Industry". *Computers & Chemical Engineering* 28(5):727–735.
- Nepal, B., M. Natarajarathinam, K. Balla. 2011. "Improving Manufacturing Process for Biomedical Products: A Case Study". *Emerald Insight* 22(4):527–540.
- Sanatela. 2020. Sanatela Website. <https://sanatelamedical.com/>.
- Stonier, A., D. Pain, A. Westlake, N. Hutchinson, N. F. Thornhill, and S. S. Farid. 2012. "Integration of Stochastic Simulation with Multivariate Analysis: Short-term Facility Fit Prediction". *American Institute of Chemical Engineers* 29(2):368–377.
- Stonier, A., M. Smith, N. Hutchinson, and S.S. Farid. 2009. "Dynamic Simulation Framework for Design of Lean Biopharmaceutical Manufacturing Operations". *Computer Aided Chemical Engineering* 26:1069–1073.
- U.S. Food and Drug Administration (FDA). CFR - Code of Federal Regulations Title 21. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271/>.
- U.S. Food and Drug Administration (FDA). 2019. Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). <http://www.fda.gov/regulatory-information/>.
- Wang B. Martagan T. Corlu C. 2019. "Stochastic Simulation Model Development for Biopharmaceutical Production Process Risk Analysis and Stability Control". In *Proceedings of the 2019 Winter Simulation Conference*, edited by N. Mustafee, K-H.G. Bae, S. Lazarova-Molnar, M. Rabe, C. Szabo, P. Haas, and Y.-J. Son, 1989–2000. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.
- World Health Organization (WHO) (2018) Cancer - Key Facts. <https://www.who.int/news-room/fact-sheets/detail/cancer/>.

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