Optimization of a 20,000 Liter Bioreactor Through Computational Fluid Dynamics Simulation Analysis

Grant Proposal

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Author Note

If needed, write notes here with an indented first line. Be mindful that the text in your grant proposal should be between 10-12 font size with a chosen font of Caibri, Times New Roman, or Arial. A Table of Contents is *optional*; however, you should format the section headers appropriately to have them show up in the TOC. Lines should be double-spaced.

Contents

Abstract (RQ) or Executive Summary (Eng)

The abstract would summarize what you (as the author) would like to convey. It would include some knowledge gaps that eventually lead to researchable questions you have identified in the field.

Keywords:

Optimization of a 20,000 Liter Bioreactor Through Computational Fluid Dynamics Analysis

Commented [A1]: This initial section is **NOT** identified as the Introduction (Hoffman, 2000, 2007) but can include a broad overview of introductory information. Thereafter, each section would be formatted according to APA heading level guideline – https://owl.purdue.edu/owl/research_and_citation/apa_style/apa_formatting_and_style_guide/apa_headings_and_seriation.html (Davidov et al., 2013; Knafo et al., 2008). Section Headers would be the same size and font as the text (Warneken & Tomasello, 2006). As a general guide, a grant proposal should start with general relevance and move towards identifying knowledge gaps in the field and potential researchable questions/needs.

As of 2021, an estimated 8.4 million people across the world have type 1 diabetes. By 2040, this number is predicted to increase up to 13.5-17.4 million cases (Gregory et al., 2022). Type 1 diabetes is an autoimmune condition characterized by the pancreas being unable to produce insulin, which is impactful, as insulin is the hormone that allows glucose from food to be absorbed and used as energy by the body. Type 1 diabetes is a fatal disease because the body becomes unable to regulate its glucose levels. Without proper treatment, this causes life expectancies after disease diagnosis drop to just 3 years (Distiller, 2014). Effective treatment for this disease began with the creation of artificial insulin in the early 1920s (Karamitsos, 2011). With artificial insulin, type 1 diabetics became able to conduct self-care and manually calculate, inject, and adjust insulin based on their specific diets. Despite this, artificial insulin still remains a costly expenditure. Despite its role as a necessity for type 1 diabetic wellbeing, prices of rapid-acting insulin have risen to $332 per vial in 2019, representing a more than 1000% increase from its cost of just $21 in 1999 (Rajkumar, 2020).

1. Bioreactors

In the field of pharmaceuticals, bioreactors are among the most commonly used technologies for product production. As referenced in Figure 1, bioreactors are often cylindrical vessels of varying size that act as controlled environments with optimal conditions for chemical or biological reactions. This technology has been applied to numerous fields, including wastewater treatment, food production, biotechnology, and pharmaceuticals. Bioreactors have revolutionized these fields because of their cost-effectiveness, less manual labor requirements, and their ability to produce high yields (Buss et al., 2017). However, several parameters and measurements are still required in order to create an optimal environment for cells. For a proper model in a detailed study, numerous measurements and data points ought to be taken and tested for system efficiency. This includes several independent factors, with a few including tank temperature, shear stress, oxygen flow, fluid flow for a homogenous mixture, etc. A few variables that can influence these factors include the dimensions and arrangements of the tank, dimensions, arrangement, speed, and arrangement of the propeller, etc. Cells often require very specific ranges of temperature, pH levels, and other factors in order to stay alive and proliferate. Because of this, bioreactors often have to be fine-tuned so that these needs can be met for the cells. To collect enough of this data to build a comprehensive model for this purpose can be extremely time consuming and costly because of the energy that bioreactors expend in order to operate and the number of iterations that are required for complete optimization (Buss et al., 2017).

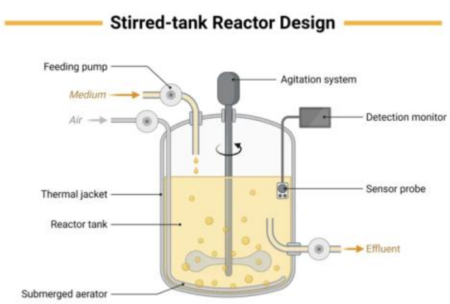

Figure 1: Diagram of a stirred vessel bioreactor. The diagram includes depictions of components that are critical to enacting and maintaining the operation of the machine. This includes the medium, air circulation, and effluent disposal valves for proper care and nutrition for stirred cells. The rotating impeller system, thermal jacket, submerged aerator, and detection device are all implemented to ensure cells are distributed uniformly throughout the entire mixture, as well as to make sure the stirring conditions stay optimal concerning liquid temperature, oxygen flow, shear stress etc. (BaiLun Biotechnology Co., Ltd, n.d.)

2. Computational Fluid Dynamics (CFD)

Current production methods of artificial insulin involve collecting insulin proteins from genetically modified strains of bacteria such as E.coli or yeast that are cultured in a bioreactor (Upreti and Lohani, 2016). This process is not specific to insulin, as an array of other pharmaceutical products are produced through bioreactors as well. In regard to the aforementioned downsides of this technology, computational fluid dynamics can address physical bioreactor model shortcomings. Computational fluid dynamics is the computer-based simulation of fluids that can be used to predict and analyze fluid flow without the need for physical testing. This process works by using software to break a fluid domain into small cells through meshing and applying fundamental equations of fluid mechanics to each cell to predict fluid movement. CFD can allow for the optimization of bioreactor models without the need of repeatedly tweaking parameters and expending time and resources to test the model again. This positive impact is further increased when applied to large scale bioreactors, which allow for increased production for decreased proportional costs (Farid, 2007; Farid, 2009; Thaore et al., 2020). Figure 2 from Farid (2009) shows these decreased upstream costs in respect to increasing bioreactor production scale. Naturally, the price for materials would increase as scale increases, yet indirect capital-related and labor costs show an inverse relationship with increasing scale. Although the exorbitant prices of insulin are due to many factors, being able to increase the yield of the product while also decreasing its cost of production can be one

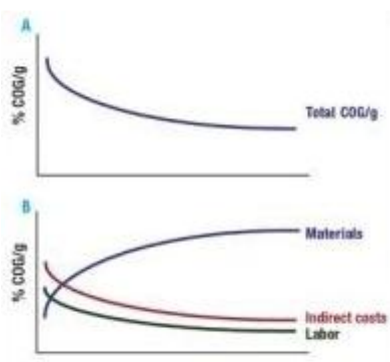

Figure 2: Comparison of cost of good per gram to increasing scale in bioreactor processes

factor in decreasing its consumer price. This beneficial impact is not solely isolated to insulin but can be extrapolated to any pharmaceutical product produced through bioreactor technology.

Section II: Specific Aims

This proposal's objective is to adjust the parameters of a 20,000 liter stirred vessel bioreactor for optimized real-world use. Our long-term goal is to simulate and establish the ideal conditions for fluid mixture and cell proliferation in a 20,000 liter stirred vessel bioreactor, where the central objective of this proposal is to use CFD simulation through COMSOL software to analyze relevant factors relating to fluid flow and cell proliferation and establish changes in the bioreactor and its elements to streamline its operation. The rationale is that optimizing bioreactors can be an intensive procedure. Computational fluid dynamics simulations employ fundamental mathematical equations relating to fluid motion. Using computational fluid dynamics can simulate the performance of a bioreactor, allowing for optimizations to be made without the need of physical testing. This is especially prevalent when applied to larger scale bioreactors where repeated physical testing and adjustments are not feasible or efficient. The work we propose here is a comparatively efficient method where its results can be directly applied to the tangible bioreactor so that it can begin operation.

Specific Aim 1: Establish dimensions of the vessel for CFD simulation

Specific Aim 2: Simulate bioreactor process through the CFD COMSOL software

Specific Aim 3: Analyze simulations and adjust parameters

The expected outcome of this work will allow for an optimized end product of the 20,000 liter stirred vessel bioreactor specific to this project.

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Commented [A4]: Some text may include an endnote identified at the sentence's end with a superscript number (Warneken & Tomasello, 2006). 1 Endnotes go at the bottom of the page, separated by a short line and formatted at a smaller size than the regular text (Reschke et al., 2017; Walle & Campos, 2012).

Section III: Project Goals and Methodology

Relevance/Significance

Using virtual simulation analysis` of bioreactor streamlining allows for a hands-off approach that eliminates the need of having to conduct any physical testing when it comes to improving the vessel's performance. This is especially relevant considering the scale of this project's bioreactor vessel being 20,000 liters in volume.

Innovation

Few studies have been published using solely computational fluid dynamics to simulate and optimize a bioreactor at this scale. Computational fluid dynamics have been commonly utilized for more common and smaller scale vessels, yet Chaudhry (2024) outlines how there are numerous barriers that prevent simple upscaling of these findings in larger ones. Even considering studies that have applied CFD to large scale vessels, nearly each bioreactor is different in its design and physical structure—even if they are of the same vessel type. This means that the analysis and optimizations that are made for one vessel does not automatically mean those findings can be applied to another with the same effect, even if they are sized similarly.

Methodology

Specific Aim #1:

Commented [A5]: Determine the …. The objective is to….. Our approach (methodology) is…. Our rationale for this approach…..

The main objective of this research is to simulate the use of the bioreactor so that adjustments and optimizations to its operation can be made. Methodology will begin with creating a 3D Computer-Aided Design drawing of the stirred vessel bioreactor. Below in Figure 1 is a diagram for visualization of what the bioreactor should look like in three dimensions. Figure 2 is a vertical cross section of the bioreactor

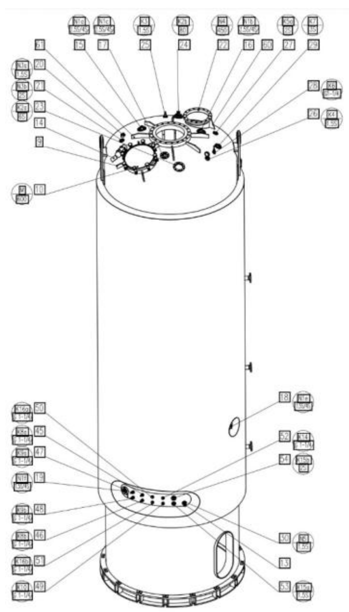

Figure 1: 3D Diagram of 20,000 Liter Bioreactor (Boston Institute of Biotechnology, n.d.)

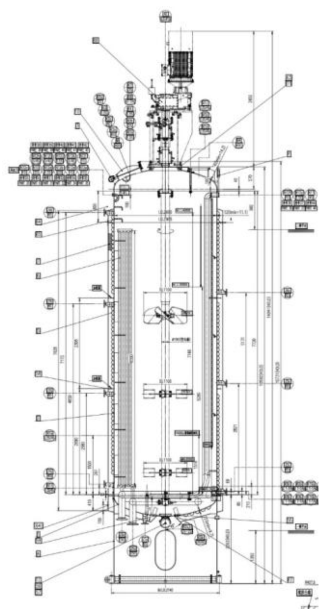

Figure 2: 2D Overlay with Parameters of 20,000 Liter Bioreactor (Boston Institute of Biotechnology, n.d.)

that provides measurements of its dimensions. Using these figures, a CAD drawing was created adhering to the vessel's dimensions. The finished CAD design of the dimensions will be used to be imported into the CFD software for model meshing.

Justification and Feasibility. Dimensions of the bioreactor need to be established for the CFD simulation in order for the model to be meshed and subsequently simulated. Using Computer Assisted

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Design for the purpose of CFD simulation is common practice where CAD programs are used to establish a simulation model (Leppänen, 2022 & Lopez et al., 2024).

Summary of Preliminary Data. For this specific aim, preliminary data includes the completed CAD drawings of the bioreactor's parameters, where all measurements are in inches. Every element of the vessel is symmetrical along the vertical dashed construction line down the center of the bioreactor. Figure 3 depicts the whole 2D layout of the bioreactor, with its total height, width, and lid height dimensions. Figure 4 shows the dimensions of the central shaft and upper propellers that are attached along it. The middle and lower propellers have dimensions identical to the ones shown in Figure 4. The dimensions of the bottom portion of the bioreactor can be seen in Figure 5, including lower propeller dimensions, bottom lid height, and distance from the base of the lid to the central shaft.

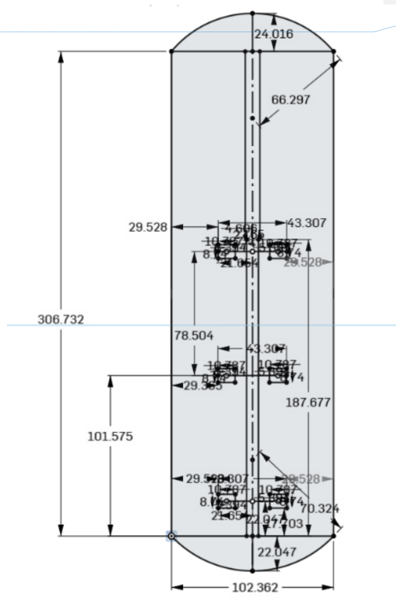

Figure 3: 2D CAD Drawing of Bioreactor (in)

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Expected Outcomes. The overall expected outcome of this aim is to allow for an accurate and importable design of the stirred vessel bioreactor to be used for CFD simulation. This knowledge will be used for creating simulations that will be as accurate to the real world bioreactor model during testing and optimization processes.

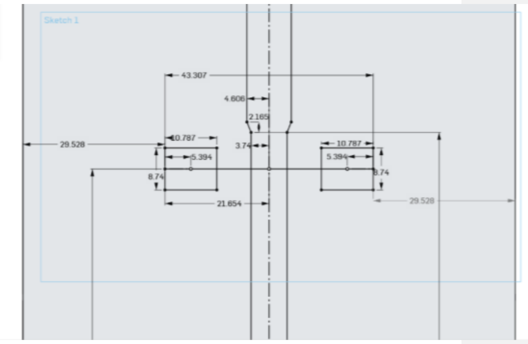

Figure 4: Dimensions of Upper Propellers (in)

Potential Pitfalls and Alternative Strategies. We expect for the import process to be seamless without issue from the Onshape to COMSOL bioreactor design import. When simulating, the results are expected to be as close to one-to-one to real-world operation as possible, yet there is potential for this to not be the case. In the simulation, this could be because of inaccurately set parameters or incorrectly designed model geometry. In the advent that this does occur, alternative strategies could include redesigning the model based on the vessel blueprints for any identified inaccuracies or tweaking suspect measurements or parameters to achieve what is expected of the vessel's operation.

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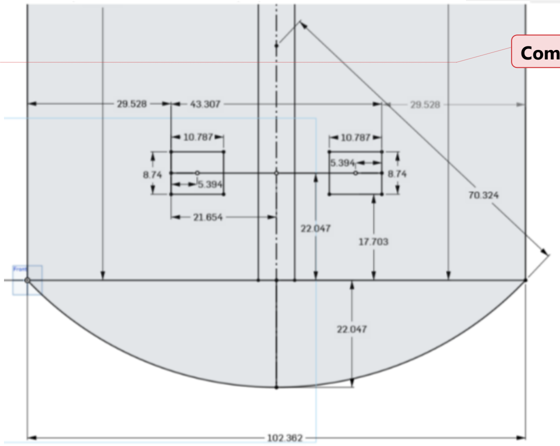

Figure 5: Dimensions of Bottom Propellers and Base (in)

Specific Aim #2:

Please follow the section format described above for an individual-specific aim.

Section IV: Resources/Equipment

Materials List:

-Computation Fluid Dynamics Simulation software (COMSOL)

-CAD platform (OnShape)

-Statistical analysis and Design of Experiment software (JMP)

Section V: Ethical Considerations

Section VI: Timeline

Section VII: Appendix

Section VIII: References

Buss, A., Suleiko, A., Rugele, K., & Vanags, J. (2017). *CFD Analysis of a Stirred Vessel Bioreactor with Double Pitch Blade and Rushton Type Impellers*. In *Proceedings of the COMSOL Conference* (2017). COMSOL. https://www.comsol.com/paper/cfd-analysis-of-a-stirred-vessel-bioreactor-with-double-pitch-blade-and-rushton-type-impellers-52431

Chaudhry, M., A. (2024). *Exploring Principles of Bioreactor Scale-Up*. BioProcess International. https://www.bioprocessintl.com/bioreactors/lessons-in-bioreactor-scale-up-part-1-mdash-exploring-introductory-principles

Distiller, L. A. (2014). Why do some patients with type 1 diabetes live so long? *World Journal of Diabetes*, *5*(3), 282–287. https://doi.org/10.4239/wjd.v5.i3.282

Fermenter. (2025). *Stirred Tank Reactor: Key Equipment for Optimizing Manufacturer Production Efficiency and Quality*. FermentorChina. https://fermentorchina.com/stirred-tank-reactor-key-equipment/

Farid, S. S. (2007). Process economics of industrial monoclonal antibody manufacture. *Journal of Chromatography B*, *848*(1), 8–18. https://doi.org/10.1016/j.jchromb.2006.07.037

Farid, S., S. (2009). Economic Drivers and Trade-Offs in Antibody Purification Processes*. BioPharm International, 2009*(7). *https://www.biopharminternational.com/view/economic-drivers-and-trade-offs-antibody-purification-processes-0*

Gregory, G. A., Robinson, T. I. G., Linklater, S. E., Wang, F., Colagiuri, S., Beaufort, C. de, Donaghue, K. C., Harding, J. L., Wander, P. L., Zhang, X., Li, X., Karuranga, S., Chen, H., Sun, H., Xie, Y., Oram, R., Magliano, D. J., Zhou, Z., Jenkins, A. J., … Ogle, G. D. (2022). Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: A modelling study. *The Lancet Diabetes & Endocrinology*, *10*(10), 741–760. https://doi.org/10.1016/S2213-8587(22)00218-2

Karamitsos, D. T. (2011). The story of insulin discovery. *Diabetes Research and Clinical Practice*, *93*, S2–S8. https://doi.org/10.1016/S0168-8227(11)70007-9

Leppänen, J. (2022). Methodology, applications and performance of the CAD-based geometry type in the serpent 2 Monte Carlo code. *Annals of Nuclear Energy*, *176*, 109259. https://doi.org/10.1016/j.anucene.2022.109259

Lopez A., Magri G., Cella U., Urso G., Della Barba F., & Biancolini M., E. (2024). Efficient Shape Optimization in Aeronautics: Integrating Parametric CAD and Mesh Morphing for Enhanced Aerodynamic Performance. *ICAS- Internaitonal Council of the Aeronautical Sciences*. https://www.icas.org/icas_archive/icas2024/data/papers/icas2024_0824_paper.pdf

Rajkumar, S. V. (2020). The High Cost of Insulin in the United States: An Urgent Call to Action. *Mayo Clinic Proceedings*, *95*(1), 22–28. https://doi.org/10.1016/j.mayocp.2019.11.013

Thaore, V., Tsourapas, D., Shah, N., & Kontoravdi, C. (2020). Techno-Economic Assessment of Cell-Free Synthesis of Monoclonal Antibodies Using CHO Cell Extracts. *Processes*, *8*(4), 454. https://doi.org/10.3390/pr8040454

Upreti, P., & Lohani, P. (2016). Industrial Production of Insulin by Genetically Modified Organism. *Asian Journal of Science and Applied Technology*, *5*(1), 20–23. https://doi.org/10.51983/ajsat-2016.5.1.2543

Deadlines and Rubric

Checkpoint/ Due Date	Looking For	Max Points
Checkpoint #1	• Meet the checkpoint on time (late work loses points) • Mind map (10pts) - includes headings and subheadings • At least one heading/subheading planned out • Filename is appropriately formatted (Crowthers Grant Proposal 2022v1), submitted to Canvas (2 pts) • Organized and formatted headers/subheaders (3 pts) • Completed two written pages of Introduction (20 pts) • At least 4 sources in the reference section, formatted appropriately (10 pts) • Appropriate in-text citations (Crowthers et al., 2022) for those 4 citations listed above (5 pts) • In-class, randomly assigned peer editing (at least 2 colleagues), with substantive comments (10 pts)	**60**
Checkpoint #2	• Meet the checkpoint on time (**late work not accepted**) • Filename is appropriately formatted (Crowthers Grant Proposal 2022v2), submit to Canvas • Correct formatting • correct formatting (5 pts) • title page (2 pts) • correct headers/subheaders (3 pts)	**50**

Checkpoint/ Due Date	**Looking For**	**Max Points**
	• page ID (2 pts) • • include at least 7 written pages (not counting reference page/title) (15 pts) • include at least 10 sources in the reference section (appropriately formatted) (8 pts) • include in-text citations for these references (5 pts) • In-class, randomly assigned peer editing (at least 2 colleagues), with substantive comments (10 pts)	
Draft #1	• Meet the checkpoint on time (**late work not accepted**) • Filename is appropriately formatted (Crowthers Grant Proposal 2022v3), submit to Canvas • formatted correctly (15 pts) • includes 7-10 pages of well-written, organized, and edited work (10 pts) • organized to help support narrative with logical flow of ideas within sentences, paragraphs, and sections • provides enough context and depth for the reader to understand what is being proposed • uses evidence to support ideas • technical control (few to no errors in grammar, spelling, word usage, punctuation, and agreement) (10 pts) • transitions used to support narrative • research/engineering plan builds naturally from the Introduction	**70**

Checkpoint/ Due Date	**Looking For**	**Max Points**
	• Corrections made to previous versions (5 pts) • ***Effectively utilize at least 2 graphs/figures/tables in the Introduction from other scientific literature (5 pts)*** • include at least 10 sources in the reference section (appropriately formatted) (10 pts) • include in-text citations for these references (5 pts) • Style: variety of sentence structure, word choice, and tone are appropriate for the topic and audience (5 pts) • Insight: analysis, inferences, and conclusions show depth and originality of thought (5 pts)	
Final Version	• Meet the checkpoint on time (**late work not accepted**) • Filename is appropriately formatted (Crowthers Grant Proposal 2022v3), submit to Canvas • The paper will be checked for plagiarism using Canvas and Turn-It-In • formatted correctly (10pts) • includes 7-10 pages of well-written, organized, and edited work (10 pts) • organized to help support narrative with logical flow of ideas within sentences, paragraphs, and sections (10 pts) • provides enough context and depth for the reader to understand what is being proposed (10 pts) • uses evidence to support ideas (10 pts) • technical control (few to no errors in grammar, spelling, word usage, punctuation, and agreement) (10 pts) • transitions used to support narrative (5 pts)	**175**

Checkpoint/ Due Date	Looking For	Max Points
	• research/engineering plan builds naturally from the Introduction (5 pts) • Effectively utilize at least 2 graphs/figures/tables in the Introduction from other scientific literature (5 pts) • ***Effectively use at least 2 graphs of preliminary testing/proof of concept testing (from your own work) in the Project Description to support your narrative (50 pts)*** • include at least 10 sources in the reference section (appropriately formatted) (10 pts) • include in-text citations for these references (5 pts) • Style: variety of sentence structure, word choice, and tone are appropriate for the topic and audience (10 pts) • Insight: analysis, inferences, and conclusions show depth and originality of thought (15 pts) • Comments from Checkpoint Draft 1 are addressed in their entirety • Strong corrective action taken (5 pts) • max point loss for not making corrections: -50 pts	