NIIMBL – SIMULATED MANUFACTURING

PURDUE UNIVERSITY | The Data Mine

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NIIMBL – The National Institute for Innovation in Manufacturing Biopharmaceuticals

BACKGROUND AND MOTIVATION

We set out to increase the ability to model the continuous manufacturing of monoclonal antibody (mAb). Typically, models for large scale production are derived from a small number of bench scale experiments but fail to account for the inherent variability in biological systems.

One example is surmised in the equation below (fig. 2), which models the relationship between high mannose glycoforms (a product quality attribute which has an upper acceptable limit) and perfusion rate in the bioreactor (a process parameter) in detail.

Goal: Based on these two key factors, we worked with NIIMBL to create a statistical model that would allow us to find a perfusion rate resulting in 95% success in achieving the target mannose level.

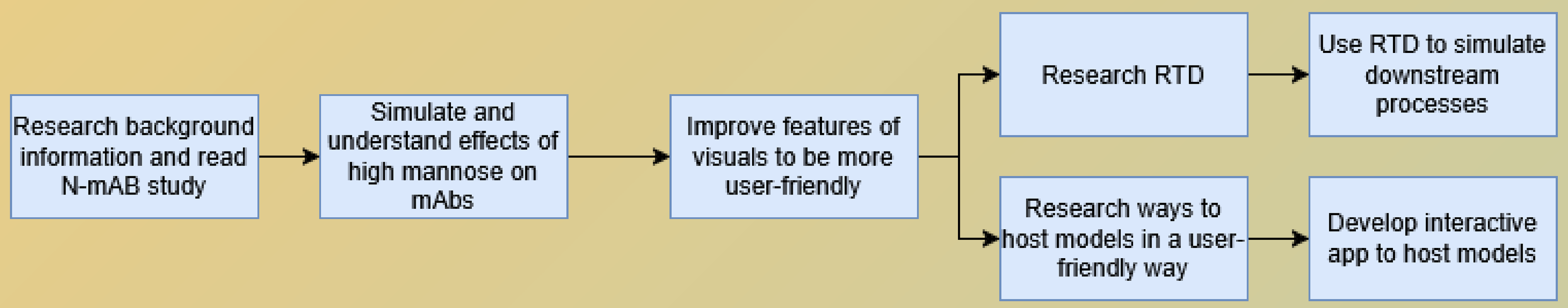

Figure 1: Timeline for Simulated Manufacturing

SIMULATING HIGH MANNOSE VALUES

- Simulation of values for high mannose values for a hypothetical monoclonal antibody
  - Exploration of the behavior of parameters given by the n-mAb case study with the 4PL function (fig. 2)
  - Creation of basic data visualization of a single simulation
  - Increasing number of simulations run (Monte Carlo)
  - Finding failure rate given by a constant failure threshold (fig. 3)
  - Calculating the best target perfusion rate
    - Testing a range of different target perfusion rates using the above model to find the failure rate for each

$$\text{High\_mannose} = c + \frac{(d-c)}{\left(1+\left(\frac{\text{Culture\_Day}}{b}\right)^{a}\right)}$$

Figure 2: Equation describing how high-mannose levels change over culture days for a given perfusion rate (d)

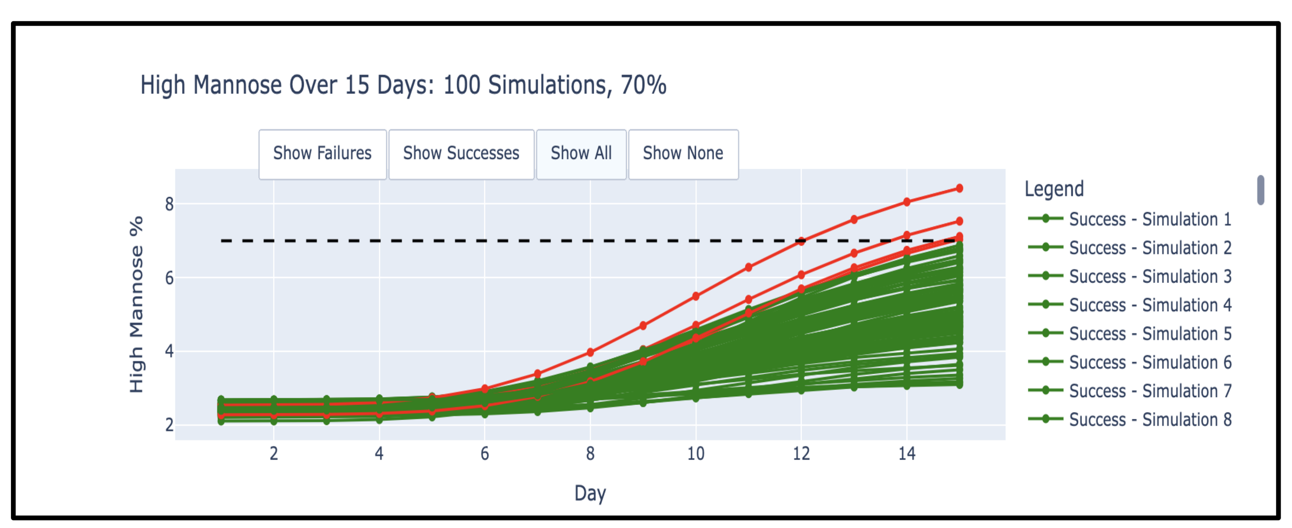

Figure 3: Displays the simulated high mannose values for a target perfusion rate of 70%

SIMULATING TIME IN TANK

- Residence Time Distribution (RTD) describes the probability distribution of how long a solid/fluid spends in a system, in our case, the system being a step of the manufacturing process
- We studied and updated RTD models from bio-rtd library used in the Sencar research paper
- We combined the top two graphs to get the bottom graph (in fig. 4)
- By convoluting, we described the effect of the RTD on the product flowing into the system to get the concentration of product flowing through the system

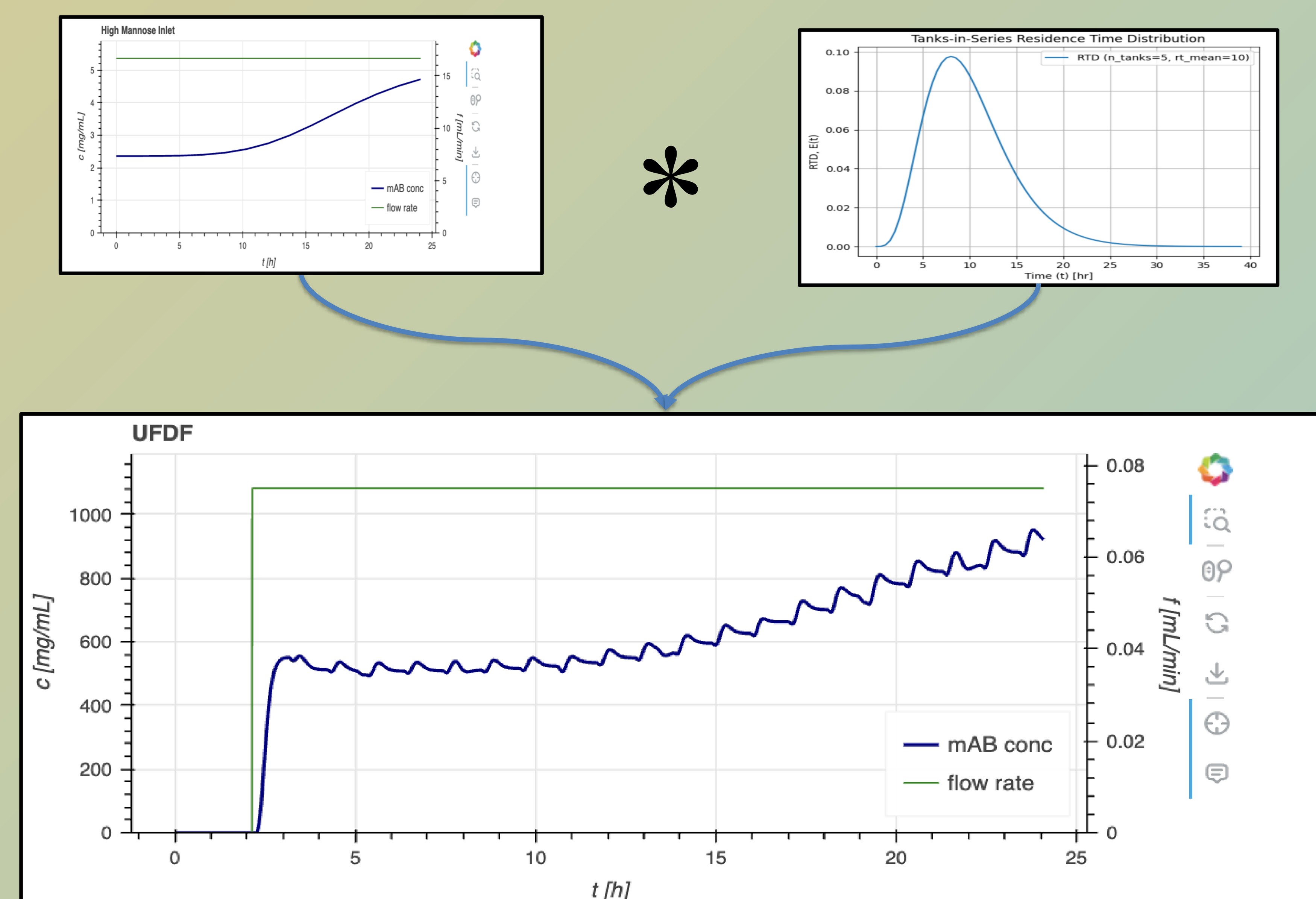

Figure 4: We simulated the downstream process by using the high-mannose simulation and convoluting it with the RTD PDF to get the mass flow graph—in this case, of the ultrafiltration/diafiltration step

APP IMPLEMENTATION

- We developed models to optimize the drug perfusion rate while ensuring high mannose levels for optimum titer
- These models were integrated into a desktop application with interactive features for enhanced user engagement
- The application includes a toggle bar, enabling users to interact with Plotly-based models and visualize key outcomes dynamically

Figure 5: QR code of video demonstration for the web-app

CONCLUSIONS

- We created models that:
  - Predict the failure rate in a biopharmaceutical simulation of high mannose percentages
  - Display how long this hypothetical protein stays in a phase and how its amount changes over time (see fig. 6)
- We built a web-app
  - with interactable features, allow the users to interact with the graphs, models and outcomes
  - Improves access for researchers and/or manufacturers to make informed decisions about monoclonal antibody production

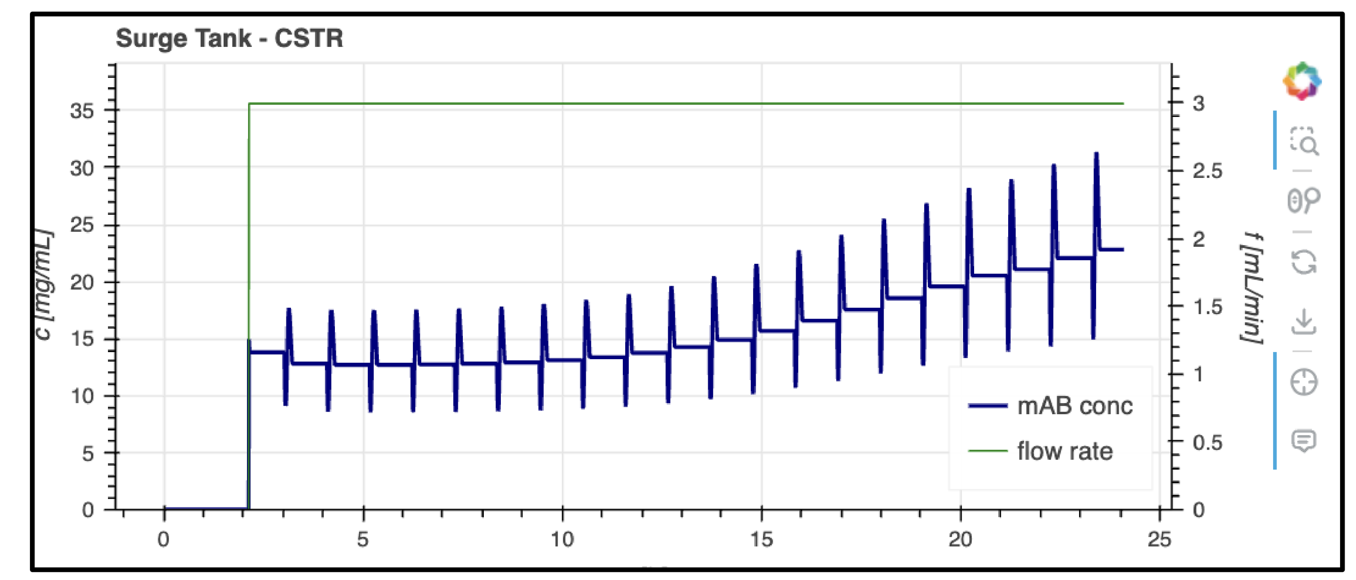

Figure 6: Another phase of the downstream process—this time, the continuous surge tank reactors

FUTURE GOALS

- Explore other parts of manufacturing process (continuous)
- Improve the interactivity and usability of the visualization tools by developing a more interactive app giving a user-friendly dashboard for stakeholders
- Conduct more extensive simulations, incorporating additional variables to simulate real-world variability

REFERENCES AND ACKNOWLEDGEMENTS

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