Development of Experimentally Validated Machine Learning (ML) Based Model to Predict the Thawing Time of Biologics during Large Scale Freeze-Thawing Cycles

Authors: Venkatraman Nagarajan (1), Dr. Bodhisattwa Chaudhuri (1,6,7), Tibo Duran (3), Tanu Mehta (1), Dr. Yangchao Luo (2), Yi Wang (2), Dr. Bruna Minatovicz (4), Dr. Lauren Fontana (5)
Presenting Author: Venkatraman Nagarajan
Affiliations: (1) Department of Pharmaceutical Sciences, University of Connecticut. (2) Department of Nutritional Sciences, University of Connecticut. (3) Eli Lilly and Company, Indianapolis, Indiana. (4) Johnson and Johnson, New Brunswick, NJ. (5) Sanofi Pharmaceuticals, Framingham, MA. (6) Department of Chemical and Biomolecular engineering, University of Connecticut. (7) Institute of Material Science, University of Connecticut.
Corresponding Author's email: bodhi.chaudhuri@uconn.edu

Purpose

Freezing and thawing (F/T) of bulk protein solutions is a common processing step used to maintain stability and high quality of biopharmaceutical products during development and production. Despite the advantages of freezing biologics, the freeze-thaw (F/T) process itself offers numerous challenges because of the poor understanding of how various process parameters affect the F/T of high concentration or viscous protein formulation. Therefore, it is imperative to better understand the mechanism and process impacts of F/T process for the development of optimized bulk F/T processes. The overall objective of this research is to develop an experimentally validated AI/ML model to predict the outcome of thawing experiment at different scales. First, an experimental approach is implemented to characterize F/T process by evaluation of different critical process parameters such as fill volume, concentration, solution viscosity and container configuration. Following that, the experimental results are used to develop an AI/ML model to predict the thawing time of large-scale biologics at different scales.

Methods

An Artificial Neural Network (ANN) based model is used to predict the thawing rates of biologics as ANN based models. Data driven ML models such as the ANN models, have been chosen as they perform well in the case of non-linear experimental data, and they also have the capability of extrapolating data to overcome the complexity and cost burden of experimental work. The input parameters such as solution viscosity, fill volume, loading distance between bottles while thawing, etc. were given to the supervised ANN model as input features and the thawing rate was extracted from the model as predictions. Multiple-input-single-output models were implemented in Matlab using the Levenberg-Marquardt (LM) algorithm. Additionally, to improve the accuracy of the model, molecular descriptors were given to the model along with other input features previously mentioned and a decision tree was implemented to filter out the most impactful molecular descriptors.

Results

The goal of the experiments was to calculate the thawing rates of proteins and protein surrogates like BSA and PEG 4000, which can be used to train the ANN models. Solutions with different viscosities were prepared using PEG 4000 and BSA. The solutions were stored in square polycarbonate bottles, frozen in a -80 °C refrigerator for 24 hours and thawed afterwards. Thawing rates (°C/min) were calculated based on temperature differences between the starting and ending points of experiments and the time taken to reach the end points from the starting points. The starting point of the experiments was the beginning of the thawing process. Two different ending points were chosen for the experiments. The first end point was the disappearance of visible ice in the bottles and the second point was the solution temperature reaching 15°C.

Conclusion
The AI/ML model was able to make predictions of thawing rate with the current experimental data. The model's performance was evaluated using the MRE for both testing and training data sets.

Keywords: Artificial Intelligence, Machine Learning, Biopharmaceutics, Freezing-Thawing