PEGylation is a generic term for chemical conjugation of polyethylene glycol (or PEG) to biomacromolecules such as proteins. PEGylation is frequently used to improve the properties of therapeutic proteins. While this type of chemical reaction is easy to carry out, it typically results in the synthesis of complex mixtures of different PEGylated forms, i.e. mono-, di-, tri-, and higher-PEGylated protein. With many PEGylated therapeutic protein products the mono-PEGylated protein is usually the desired form. Formation of by-products in a PEGylation reaction represents material loss as well as the inconvenience of a challenging purification process that would follow. The problem of low selectivity of mono-PEGylation could be addressed through the use of specific reactions such as N-terminal PEGylation. However, even with such specific reactions, significant amounts of by-products are typically synthesized. Generally speaking, a trade-off between selectivity and yield of desired product is observed in most PEGylation reactions. In [1], we presented a systematic attempt at optimization of batch protein PEGylation. To this end, initially a first principles model (with the associated reaction network) was presented with kinetic rate constants determined using the experimental data. The dynamic model captures the effect of variation in initial condition as well as the pH at which the experiment is run. Having established the validity of the model beyond the fit data by additional experiments, the model is then utilized to determine the optimal pH, duration and initial recipe that maximize the formation of the mono-PEGylated product. The benefits of operating at the conditions suggested by the optimization problem are finally demonstrated though additional experiments.

In this contribution, we present several additional simulation and experimental results that validate both the structure and values of the identified parameters as well as explore additional means of operations. In particular, simulation results are generated to predict the productivity and yield for a fed-batch operation with parallel filtration of the reaction media. In addition, the rate kinetics are utilized in predicting operation using hollow fibre membranes for carrying out the reaction and separation. In summary, the experimental results are used to verify the structure of the proposed kinetic model, while the simulation results are used in an optimization framework to suggest optimal experimental operating conditions that are subsequently verified experimentally.

References

[1] X. Shang, B. Corbett, P. Mhaskar, and R. Gosh. Optimization of protein pegylation. AIChE Annual Meeting San Francisco, CA, 2013.