**Data-driven optimization of a freeze-drying unit using design of dynamic experiments**

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**1. Introduction and methods**

Freeze-drying (lyophilization) is a unit operation commonly used in the biopharmaceutical industry to extend shelf-life of drugs in aqueous solution. Due to the very low temperature and low pressure, it is energy intensive and time-consuming [1,2]. Adoption of time-varying inputs (namely, shelf temperature and chamber pressure) allows faster operation [3,4], but finding the optimal input profiles experimentally is not trivial, because constraints exist on product temperature and sublimation rate. A recently developed detailed first-principles model of the process may help virtualize it [5]. However, optimization of the process performance using this knowledge-driven model is computationally expensive, due to model stochasticity.

In this study, a data-driven approach to process optimization is developed by designing time-varying inputs through design of dynamic experiments (DoDE) [6]. The first-principles model is used to carry out the designed experiments, through which one can calibrate appropriate response surface models (RSMs) describing the main response variables of the process. The best trajectories of the manipulated inputs are calculated by optimization from the RSMs, which are computationally inexpensive. Results are then compared with the direct optimization of the first-principles model.

**2. Results and conclusions**

Both optimization approaches (via first-principles or data-driven modeling) allowed reducing the duration of the freeze-drying operation significantly with respect to a time-invariant recipe (Figure 1). In particular, the data-driven approach is shorter by 15%, while the knowledge-driven one by 26%. However, the data-driven approach required about one-third of the computational time of the knowledge-driven approach. For the data-driven approach, the main drawback was related to a slight violation on the constraint of the maximum product temperature. This behavior was expected as no prior input-output relationship was available when the DoDE exercise was carried out, thus making its RSM slightly less accurate. This explains also why the duration is slightly increased with respect to optimization using the first-principles model.

From a general perspective, the data-driven approach can be very useful when dealing with complex models such as the one used in this case study, with results comparable to the knowledge-driven approach, but achieved in a much shorter computational time.



**Figure 1.** Maximum product temperature profiles for the time-invariant recipe and the two optimization approaches. End of sublimation is represented by a vertical line. Upper constraint is represented by the dotted gray line.

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