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Defining process operating space under uncertainty: Bayesian Design Space for complex kinetic reactions

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Design of experiments for process scale-up can be described as a double-edged sword for the pharmaceutical industry: intensification of experiments expands the knowledge of the process (uncertainty reduction) but increases resource expenditure. On the other hand, moving forward without enough process understanding is the first stone in a path of deviations, lack of quality, and even safety concerns.
In the past years, Bayesian sampling methodologies have surfaced to incorporate uncertainty and lead to better guided risk/optimal decision making in terms of process conditions, and reduction of required experiments. Utilizing Bayesian sampling for design space offers several significant advantages: First, it allows for the incorporation of prior knowledge, leading to more informed and efficient experimental designs [1]. Secondly, by continuously updating beliefs with new data, Bayesian sampling enables a dynamic and adaptive approach, enhancing the accuracy and reliability of results. This method also provides a rigorous framework for quantifying uncertainty, ensuring robust decision-making even in complex scenarios [2]. Additionally, Bayesian sampling can effectively identify the probability space with reduced experimental work, leading to an earlier definition of a Normalized Operating Range (NOR) within a scale-up approach to a pharmaceutical process.
In this work, a batch gas generating process with 10 different reactions occurring (reagents, products and by-products) is evaluated with the proposed Bayesian Design Space [1], with different process parameters defined (time, temperature, reagent“A”initial concentration and reagent/solvent “B”initial concentration) and consumption CQA’s required for the same process. The results showed that a reduced amount of experiment (less than 6) were required to achieve an acceptable NOR for the process, and the outcome allowed for a safe transfer to a higher volume unit (manufacturing) with all safety and quality requirements achieved.
[1]–Kusumo, K. et al.,“Bayesian Approach to Probabilistic Design Space Characterization: A Nested Sampling Strategy”, I&EC research, 2019
[2]–Kennedy, P. et al.,“Nested Sampling Strategy for Bayesian Design Space Characterization”
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