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Statistical Machine Learning for defining the Design Space

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The ICH Q8 guideline [1] emphasized the Quality by Design (QbD) approach, according to which quality should be built into the product since its conception. A key component of the QbD paradigm is the definition of the Design Space (DS), defined as the multidimensional combination and interaction of inputs variables that have been demonstrated to provide assurance of quality. Besides, Rozet et al. [2] pointed out that a meaningful DS must account for uncertainty and correlation. In this sense, we distinguish two approaches:
The first approach is based on a predictive (forward) approach, such as Bayesian modeling [3] and Monte-Carlo simulations, which requires the discretization of the input domain, and then the determination for every discretization point to belong to the DS. In these cases, we strongly recommend the use of latent variable models, to project the input space onto a low-dimensional space, which allows accounting for the correlation from the past.
The second approach is based on the Partial Least Squares (PLS) model inversion [4] where model-parameter uncertainty is also back-propagated (backward approach). This approach provides an analytical representation of the DS with the additional benefit of being computationally less costly.
These methodologies are illustrated by an industrial process.

[1] ICH Harmonised Tripartite, "Guidance for Industry Q8(R2) Pharmaceutical Development."2009.
[2] E. Rozet, P. Lebrun, B. Debrus, B. Boulanger, and P. Hubert, Trends Anal. Chem., 42,157–167,2013.
[3] G. Bano, P. Facco, F. Bezzo, and M. Barolo, AIChE J.,64,2438–2449,2018.
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