Developing and optimizing analytical chromatographic method in a Quality by Design environment. Bayesian multi-criteria risk-based Design Space to guarantee future quality.

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1 Introduction

According to ICH guidelines Q8 (on Pharmaceutical Development), Q9 (on Quality Risk Management), and Q10 (on Pharmaceutical Quality System), the development of pharmaceutical analytical methods should follow the concept of Quality by Design (QbD). This means the methods are developed in order to provide quality with regards to Critical Quality Attributes (CQAs) that are defined as targets that must be reached with high guarantees, in the future use of the methods. The risks that the methods will not be of such quality should also be assessed.

Typically, a chromatographic method must provide well-separated peaks, in a short analysis time. This represents the very purpose of the method and these separation (or resolution) and run time can be viewed as CQAs. Usually, optimization systems for such methods are able to provide analytical conditions that are more suitable than others to achieve quality. However, the guaranteed and risks about the predicted quality are generally not included in the provided solutions.

2 Design Space methodology

To answer this problem, ICH Q8 goes further, defining the concept of Design Space (DS). The DS of an analytical method is defined as the set of factor settings providing satisfactory results for the CQAs. This is a risk-based methodology aiming at identifying, in the space of factors, a region that will likely provide satisfactory results in the future routine. This is achieved by means of design of experiment and response surface modeling.

First, the joint predictive density of the responses (retention times) is derived from the Bayesian posterior density of parameters of a multivariate model. Second, an adapted multi-criteria perspective is added to estimate the joint probability (i.e. guarantee) that the CQAs will reach some predefined acceptance limits. These later are defined regarding to the minimal quality one wants to achieve. For instance, a minimal separation of 0 min. for the critical pair of a chromatogram is synonym of quality. In this case, peaks are baseline resolved.

To fulfill this optimization purpose, a Monte-Carlo simulation (MCMC) is carried out to numerically propagate the predictive uncertainty of model responses and measurements to finally identify the DS, possibly under constrained responses. An example based on high-performance liquid chromatography (HPLC) methods is given, illustrating the applicability of the methodology.

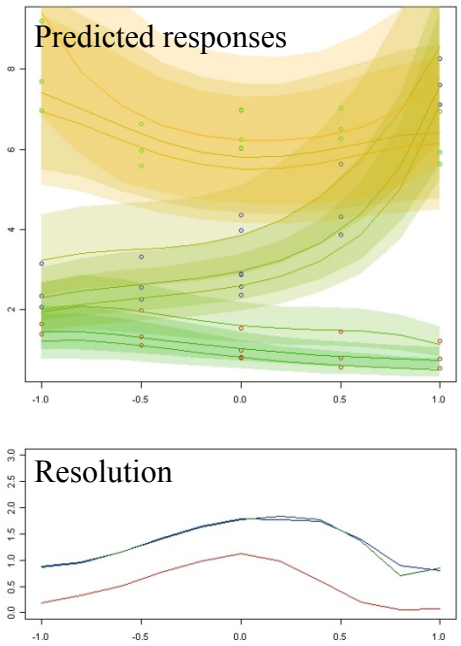

Figure 1 - (Top) Mean predicted responses (lines) and bayesian predictive intervals (shaded) for the modeled responses w.r.t to one factor, the pH. (Bottom) Mean and Median resolution computed from the predicted responses (blue, green) with the lower bayesian predictive interval (red).

3 Conclusion

We then proposed an approach for optimizing chromatographic methods (or any other processes) in a QbD environment. We emphases the provided solution to be risk-based, allowing a better understanding of the method and a good assessment of its future behavior.

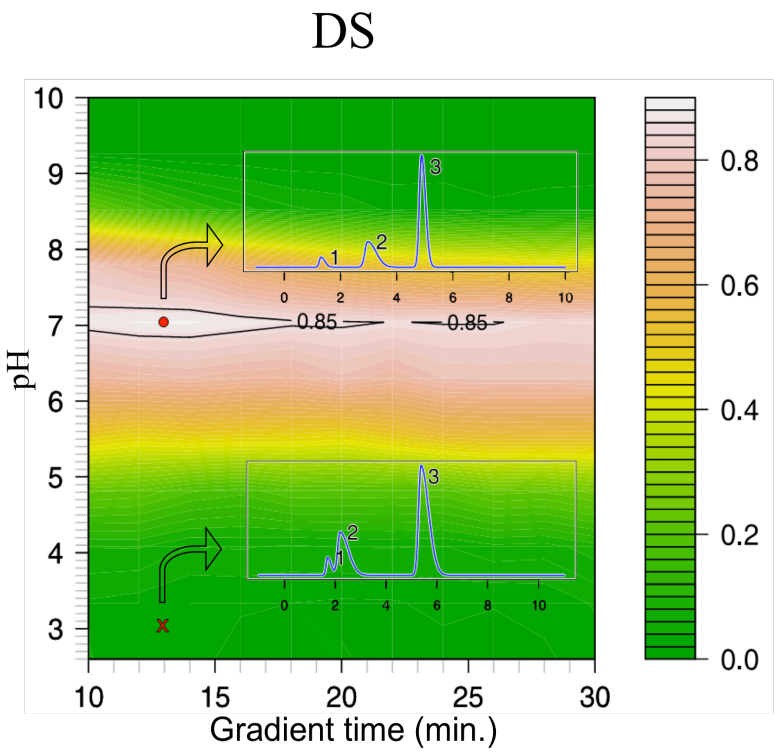

Figure 2. Probability map showing the guarantee the CQAs are within acceptance limits, in the experimental domain of two factors of interest, the gradient time and the pH of mobile phase. The white region is the set of factor settings where the probability to achieve limits on the CQAs is greater than a predefined minimal quality level of 0.85. This defines the Design Space of the chromatographic method. Within the DS, the observed chromatogram provides a good separation, while outside, the resulting chromatogram shows coelutions.