

# Title: "A Comparative Analysis of Design Space Optimization Strategies for identifying High-Volume Hypercubes, including a novel algorithm"

The search for optimal design space involves delineating a hyperdimensional volume within which all process parameters, when confined, ensure outgoing product quality remains within specifications. This work addresses the complex optimization challenge of identifying the largest possible hypercube encapsulated within a given design space. Traditional methods reliant on multidimensional grids and iterative expansion have proven computationally intensive, both in terms of iterations and memory requirements.

In response, a recent advancement has been to frame the problem as a double nested optimization challenge solved via a simplex-based derivative-free hill descent optimization algorithm. This approach seeks to maximize the hypercube's corners while ensuring the innermost quality points meet predefined quality thresholds, thus filtering out suboptimal volumes.

Building upon this premise, our investigation integrates a stochastic search algorithm to (1) mitigate the risk associated with local optima, a known pitfall of hill descent methods, and (2) facilitate the identification of multiple high-volume hypercubes. This methodological enhancement has the potential for unveiling numerous viable solutions where traditional techniques may only pinpoint a singular optimal solution.

Comparative analysis with commercial software solutions such as MODDE (Sartorius) and JMP (SAS) are provided.

This research contributes to the ongoing dialogue on design space selection strategies by providing a comparative lens through which different software or algorithms may help CMC engineers come up with process control specifications.

*Authors:* Y. Van Haelst, Yannick (Belgium) ; V. Taillefer(France) ; M. Corbera(France).

**Authors background:** Y. Van Haelst and V. Taillefer are both expert CMC statisticians in global CMC development at Sanofi. Their roles are principally in Biologics. Y. Van Haelst has a university background in Biochemistry and Informatics and 16 years CMC experiences in QA, manufacturing, and development, in small and large molecules area. V. Taillefer has a university background in statistics and 14 years experiences in CMC Bio-statistics. M. Corbera was a master student internship who worked alongside Y. Van Haelst on the algorithms an implementation in R. She graduated in 2023 as Bio-Engineer with master specialization in Applied Mathematics.