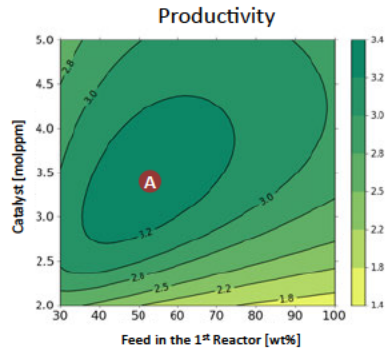


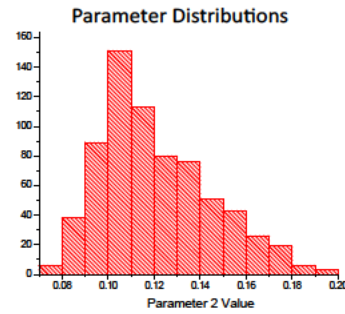
Design Space Map (w/o Uncertainty)



A Highest productivity Region

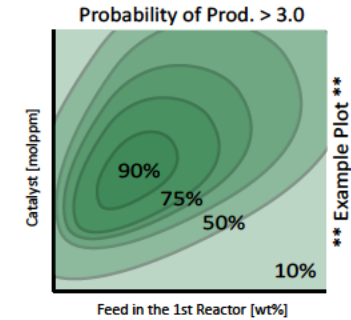
- Using the nominal model with best-fit parameters, a primary Design Space Map can be constructed to optimize process design. However, this does not take model/data uncertainty into account.

Estimate Uncertainty in Model Parameters



- Propagation of uncertainty to Design Space Maps requires quantifying uncertainty owing from; (a) model structure, and (b) experimental data.
- Model-based uncertainty (non-identifiability) is typically assessed via Multi-Start Parameter Estimation, whereas variability in data is typically assessed via sampling methods such as Bootstrapping.

Design Space Map (with Uncertainty)



- Final Design Space Maps are constructed, integrating the results of many possible singular Design Space Maps (each deriving from a single param. set)
- Statistical probabilities are assigned based upon the likelihood of achieving a specified outcome across all sampled models.



QBD SUBMISSIONS TO THE FDA FOR MANUFACTURING

Typical Resource Requirements

Experiments	~ 3 - 15
Synthetic Data Sets	~ 1,000
Parameters Estimations	~ 1,000
Simulations	~ 1,000,000
Cluster CPU #	~ 50 - 300
Total Run Time	~ 1 - 3 Days

Value Added

- Accounts for both sources of uncertainty (data & model), attributes parametric variability accordingly, and propagates uncertainty to critical process outputs.
- Assigns statistical probabilities to outputs in Design Space Maps, building confidence in overall process operation.
- Fulfills Quality by Design (QbD) mandate advanced by the FDA in the production of pharmaceutical APIs.