Bayesian Approach to Specification of Design Space

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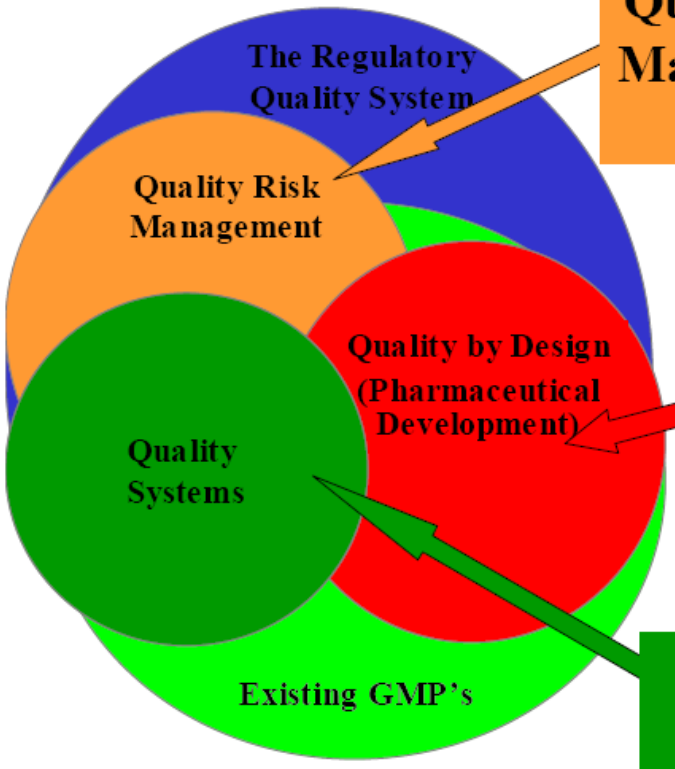
userR! 2009 (July 8-10, 2009)

inference
from Blue Reference

Quality by Design: Pharmaceutical Quality Vision

Pharmaceutical Quality Vision

Develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science.



Quality Risk Management (Q9)

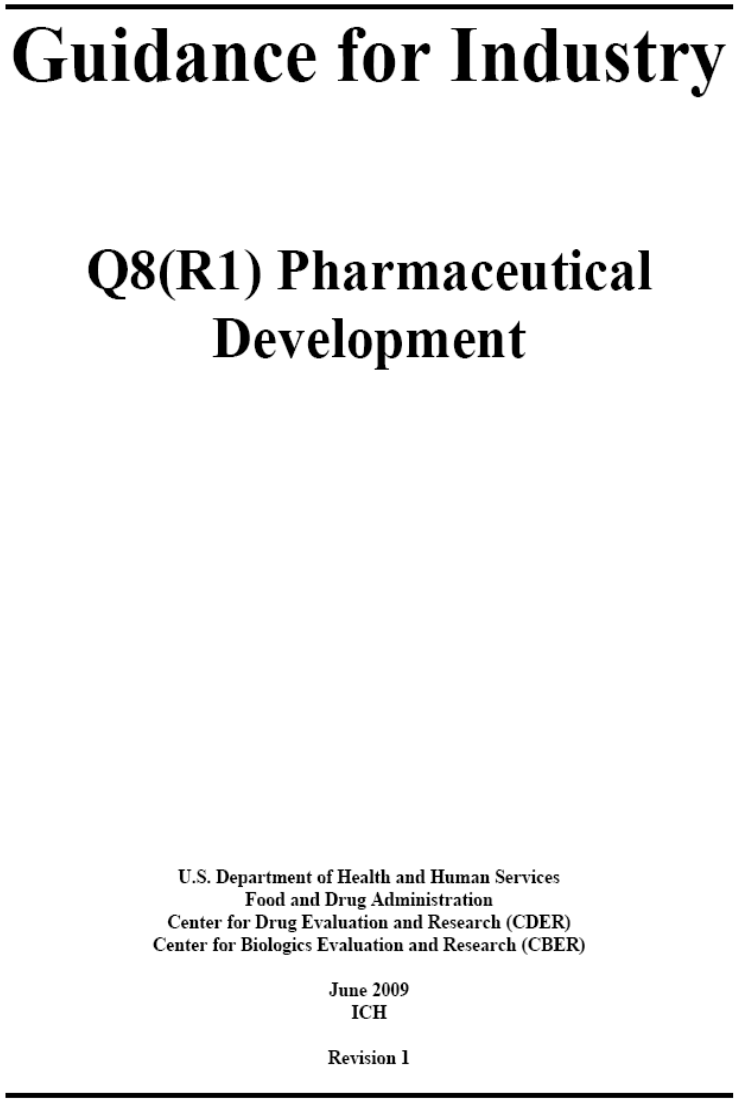
Quality by Design (Q8)

Quality Systems (Q10)

For companies with :
1. **Good design and control strategies**
2. **Good Risk Management strategies**
3. **Good Quality Systems**

Reduced regulatory burden:
- **Reduction of submissions on changes/variations**
- **Inspection of quality systems**

Pharmaceutical Development



Guidance for Industry

Q8(R1) Pharmaceutical Development

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2009
ICH

Revision 1

- QbD Pharmaceutical Development
  - Quality Target Product-Profile
  - Critical Quality Attributes (CQA)
  - Risk Assessment: link to Product CQA
  - Design Space
- What is Design Space
  - "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters **that have been demonstrated to provide assurance of quality**."
  - "Working within the design space is not considered as a change."
  - "Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process."
  - "Design space is proposed by the applicant and is subject to regulatory assessment and approval."

Quality by Design Workflow

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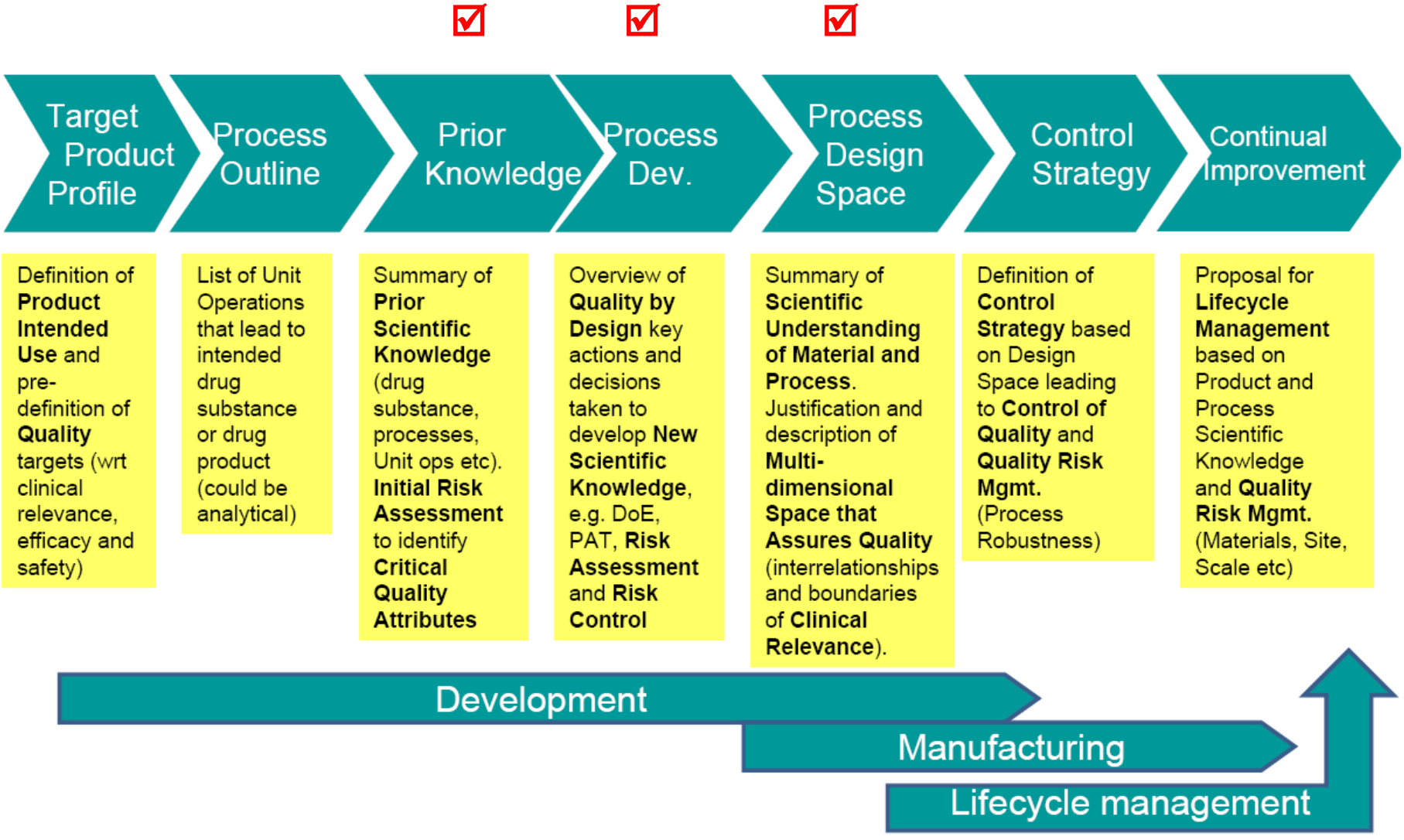

Elements of Design Space

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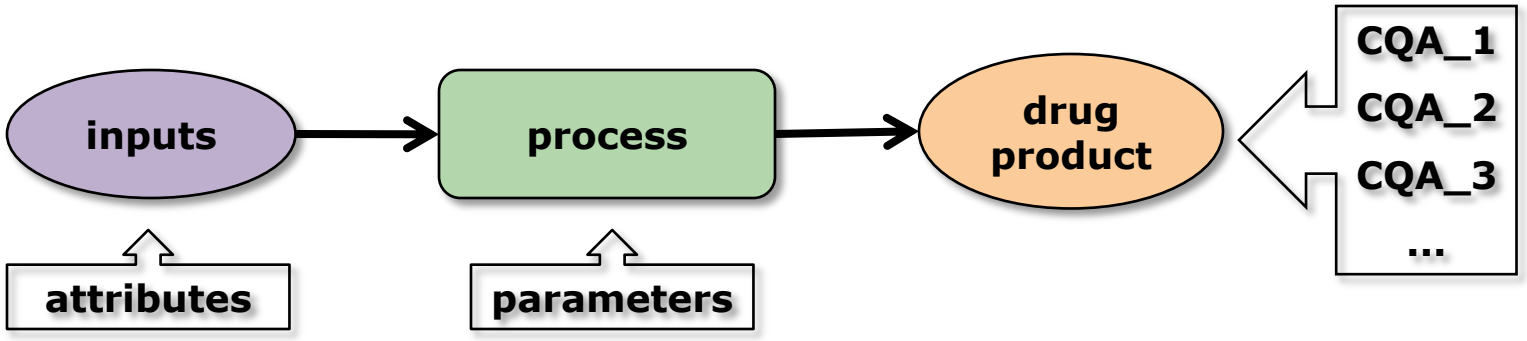
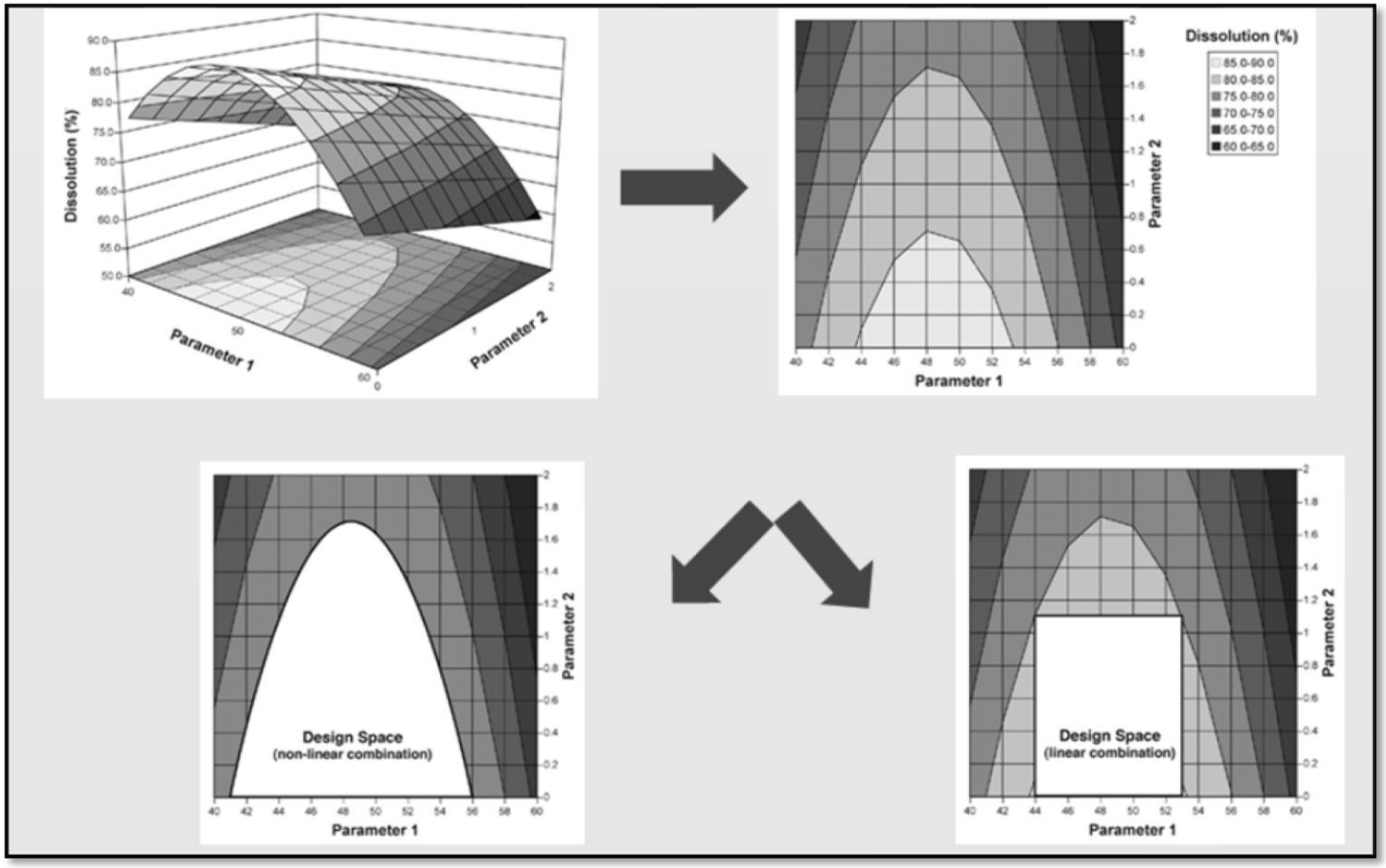
- Risk based approach to assurance of quality
- Critical to quality attributes (CQA) are multivariate
- Quantitative model links input attributes and process parameters to CQAs
- Model quantifies risk of not meeting CQAs



Q8(R1) Example Design Space



Q1. How do we enable a risk-based approach to design space?

Q2. How do we best construct the design space?

Q3. How do we assess the reliability (assurance) of the design space?

Risk-based approach to Design Space

Design Space Strategy

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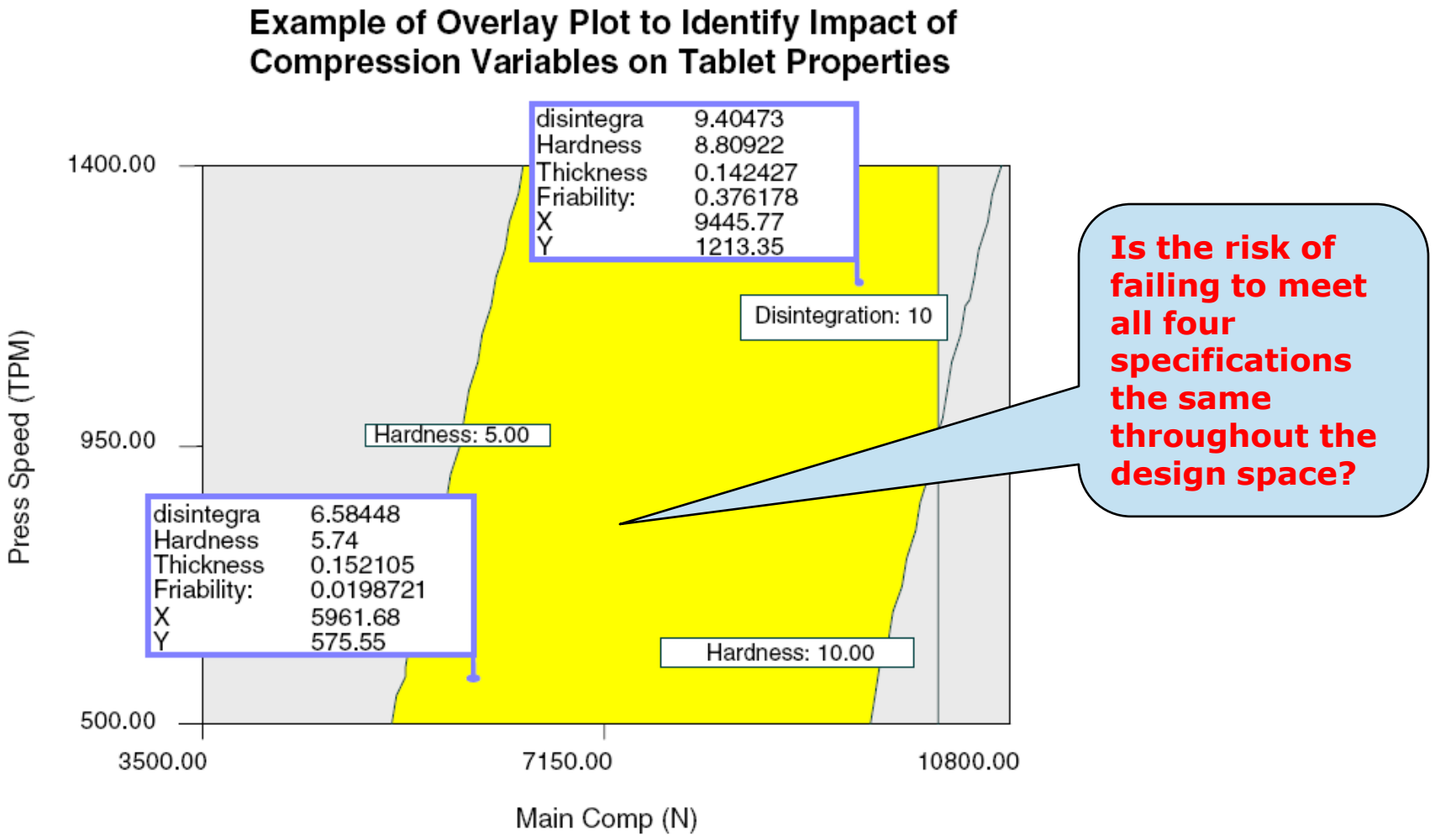
- Multivariate Strategy:
  - multidimensional combination and interaction of material and process variables linked to responses
  - responses comprised of drug product critical-to-quality attributes (CQA)
  - drug products involve a multitude of specifications (response factors)
- Overcome Limits of Conventional Design Space:
  - model: predictive response surface
  - model parameters: static variables
  - multiple responses: overlap of mean-response surfaces
- Apply Bayesian Design Space:
  - model: posterior predictive probability function
  - model parameters: random variables
  - multiple responses: multivariate joint probability function

Issue with Conventional Design Space



J. Lepore and J. Spavins, "PQLI Design Space," *J. Pharmaceutical Innovation* (2008) 3:79-87

Why Multivariate & Bayesian?

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from Blue Reference

- Multivariate because
  - Quality entails multiple responses (CQA defined by specifications)
  - Multiple responses are not independent
  - Correlation between responses can have a big effect on probability of meeting all specifications
- Bayesian because conventional
  - fails to account for uncertainty in model parameters
  - fails to account for correlation structure in data
  - fails to provide a metric for "assurance of quality"
  - fails to enable use of prior information
  - fails to enable adaptive experimental design

Illustrative Example: Process for Coating Polymer

Multivariate Chemical Process

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- Chemical Process
  - Production of a coating polymer
  - Two critical to quality attributes (CQA)
    - Response 1: Percent conversion
    - Response 2: Polymer viscosity
  - Two critical process parameters
    - Parameter 1: reaction time
    - Parameter 2: reaction temperature
- Product profile: target CQA
  - Percent conversion: > 68%
  - Viscosity: 40 ± 2 mPA-secs

Bayesian Response Surface Model

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- Experimental Design
  - Central composite design
  - 8 setting combinations (4 corners and 4 faces of a square)
  - 5 centerpoints
- Models
  - Response surface models for conversion and viscosity
  - linear, cross-product and quadratic terms for each response
- Bayesian Regression and Analysis in R (R-project)

MCMC Bayesian Regression

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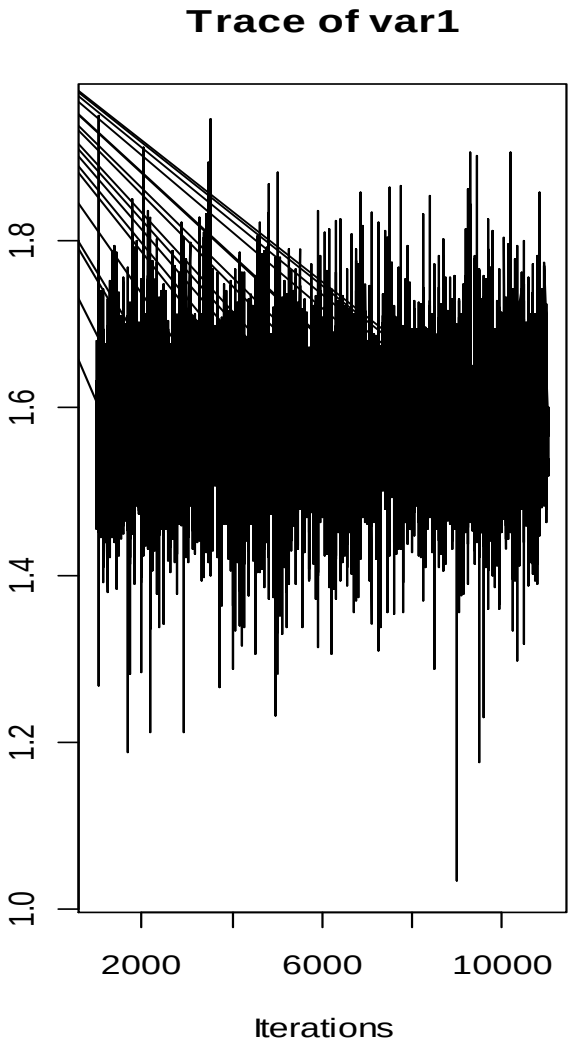
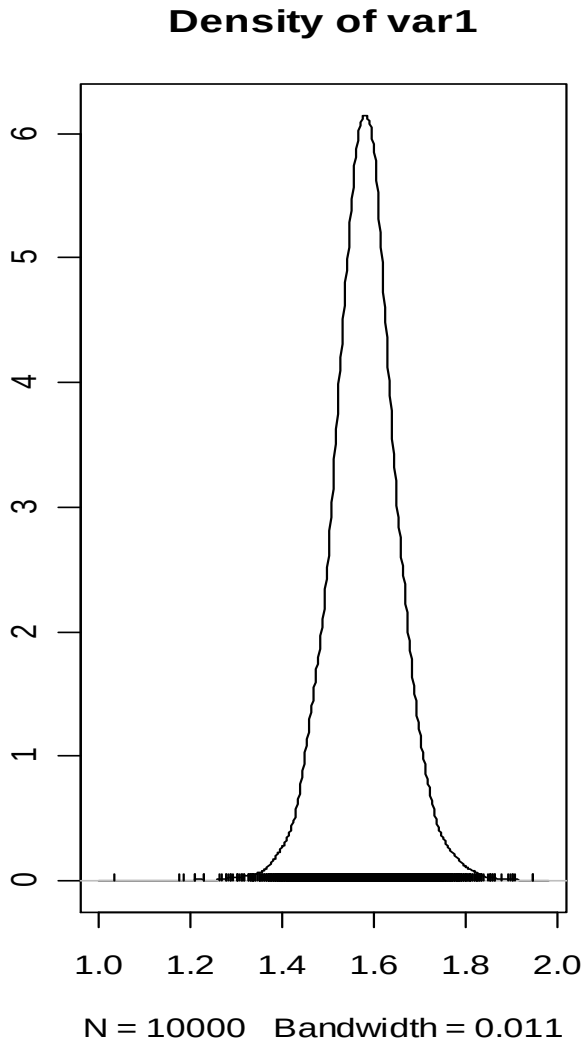
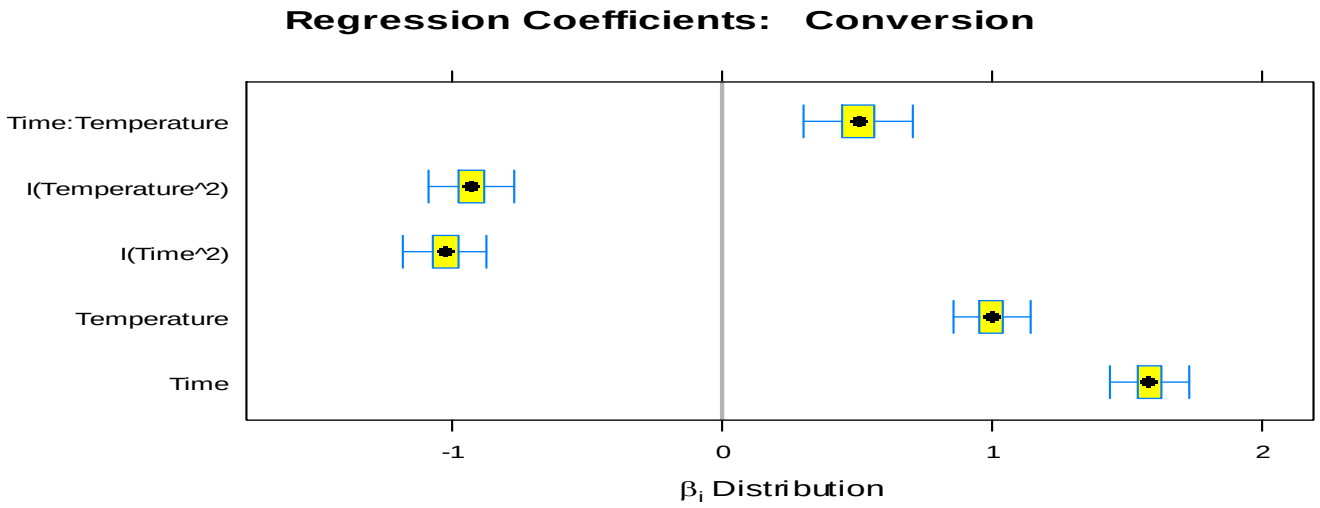
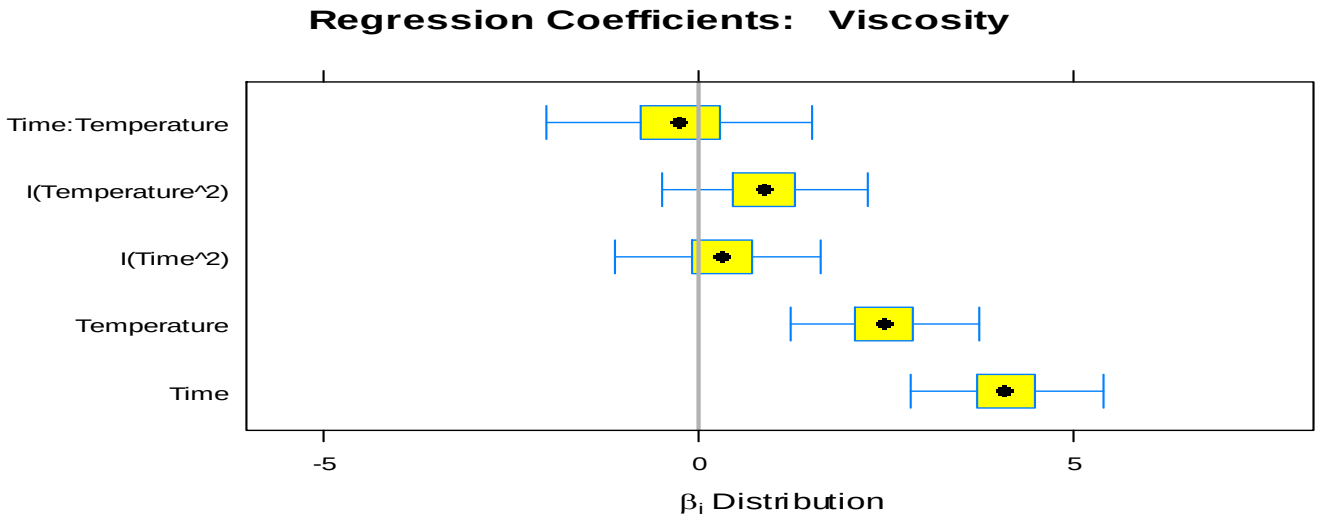


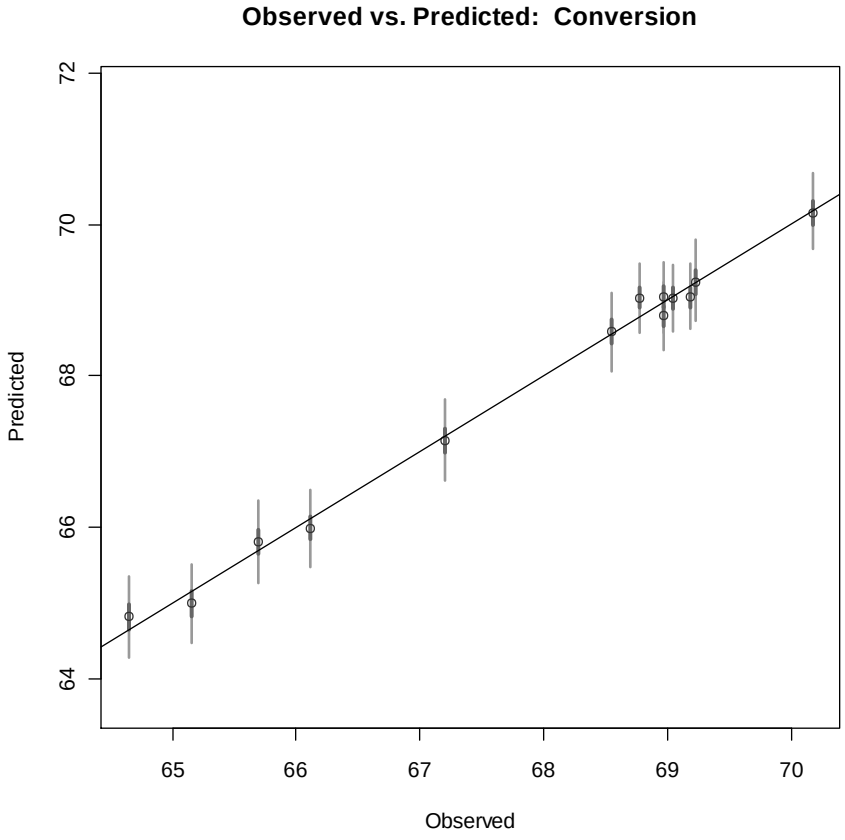


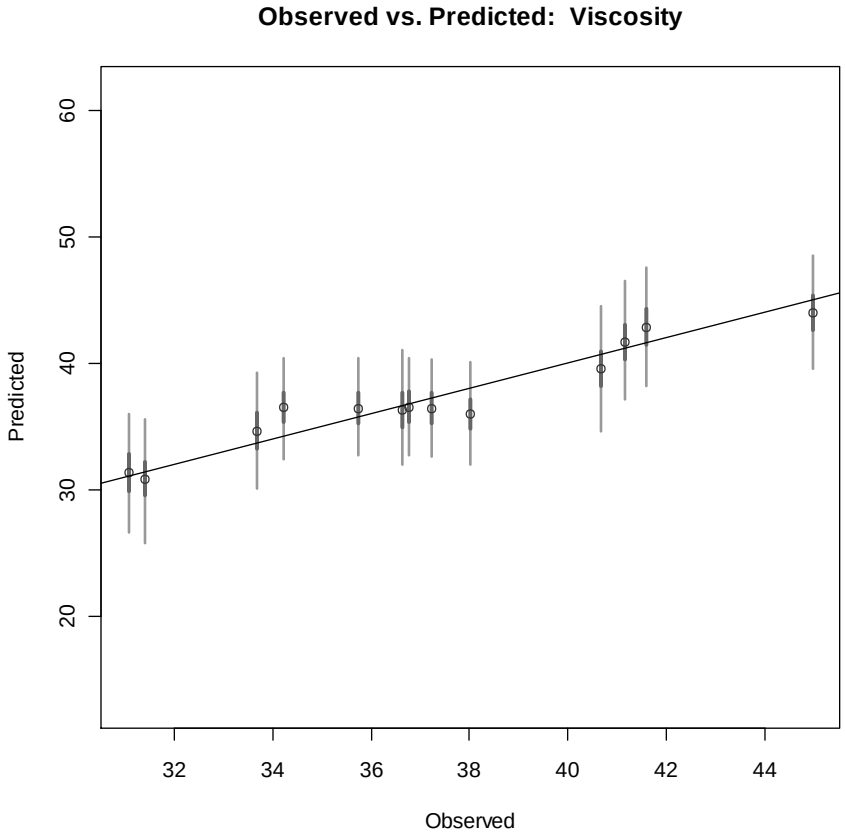
Model Coefficient Distribution



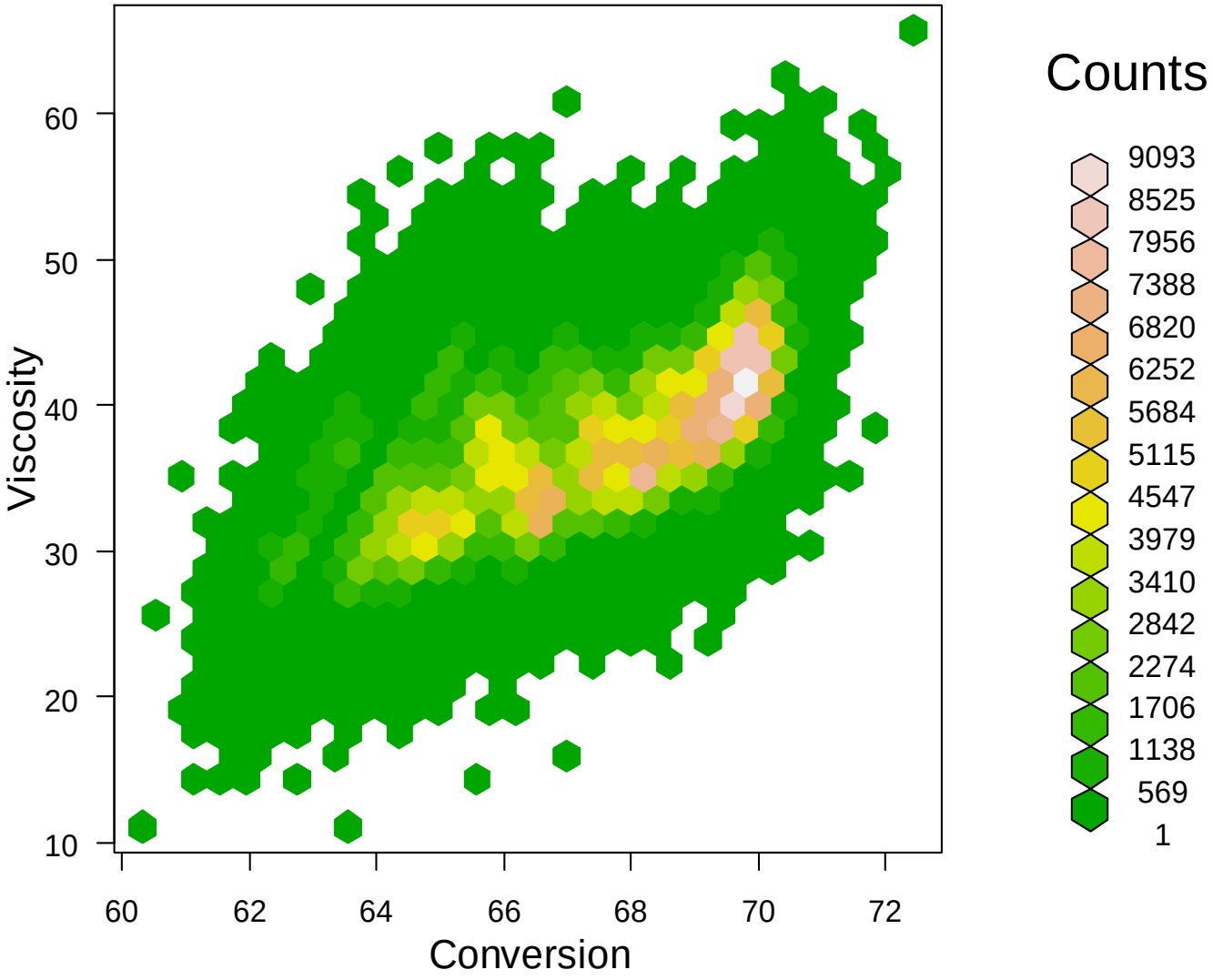


Posterior Distributions





Knowledge Space



95% Credibility Intervals

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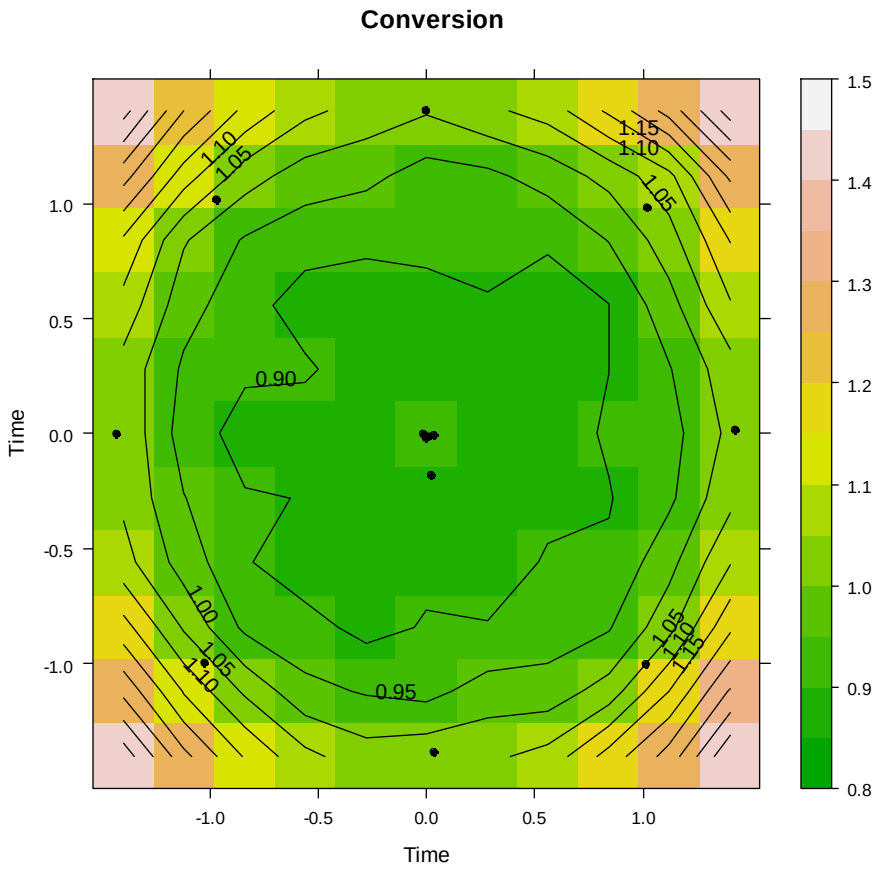
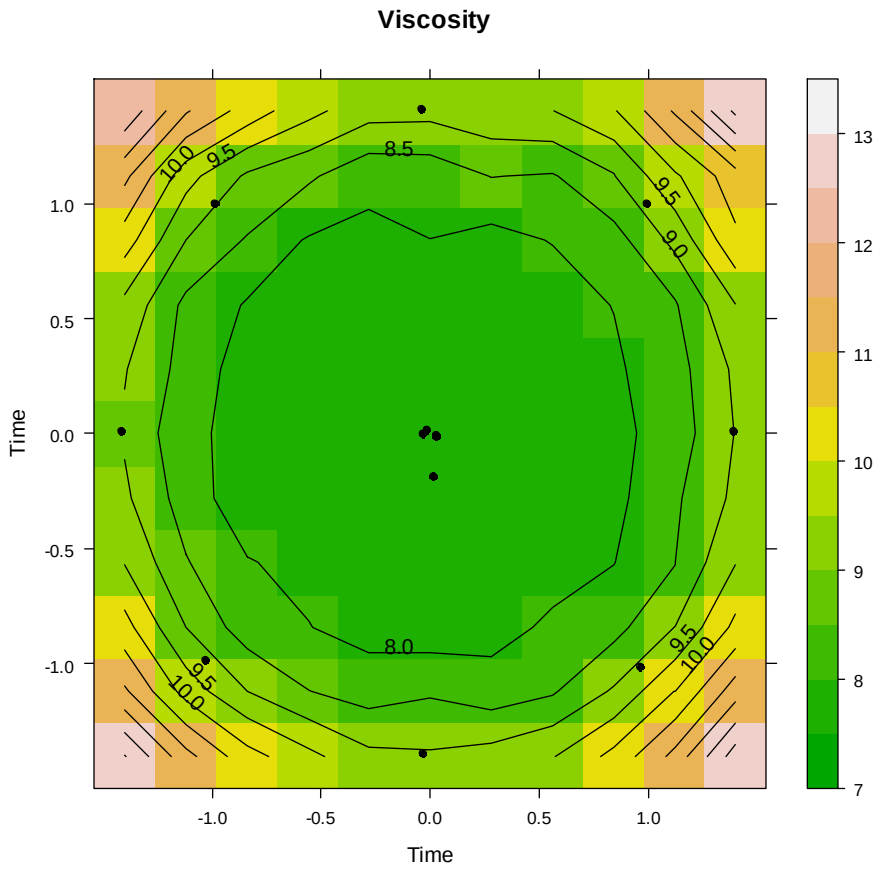
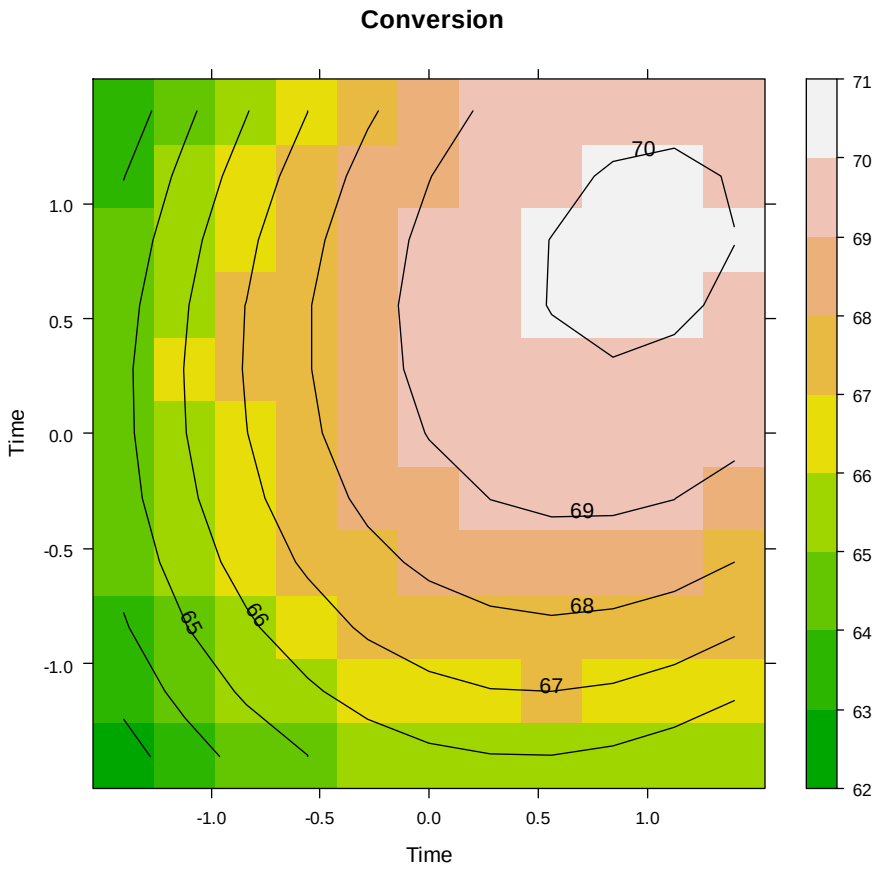
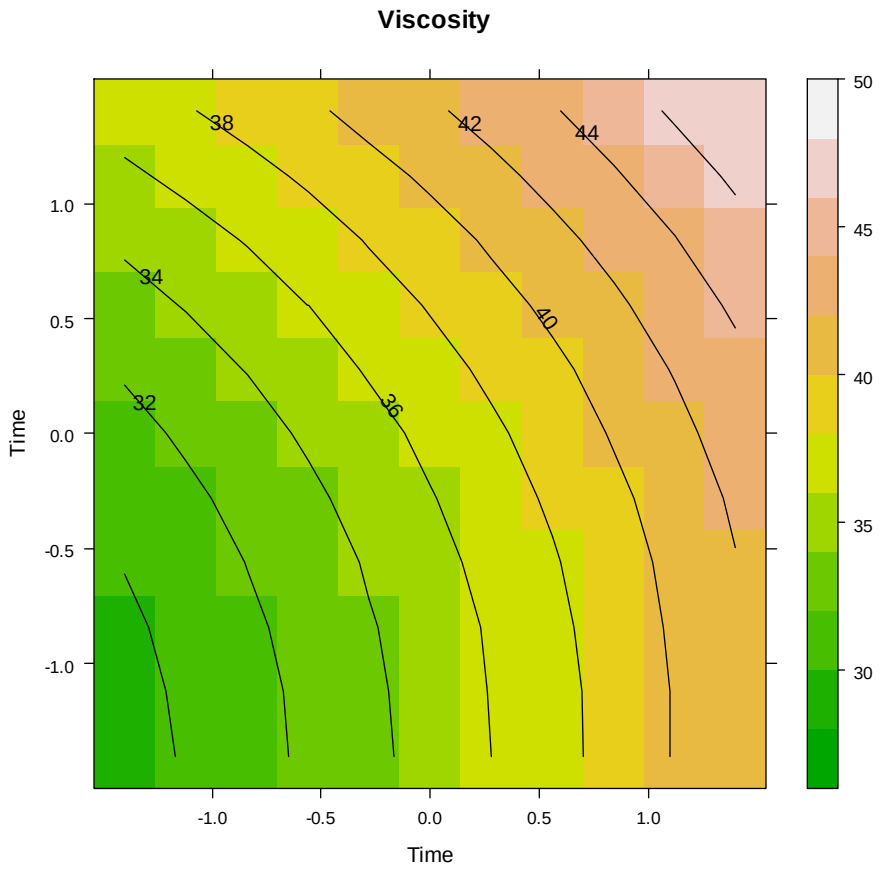




Mean Response Plots





Response Probability Distributions

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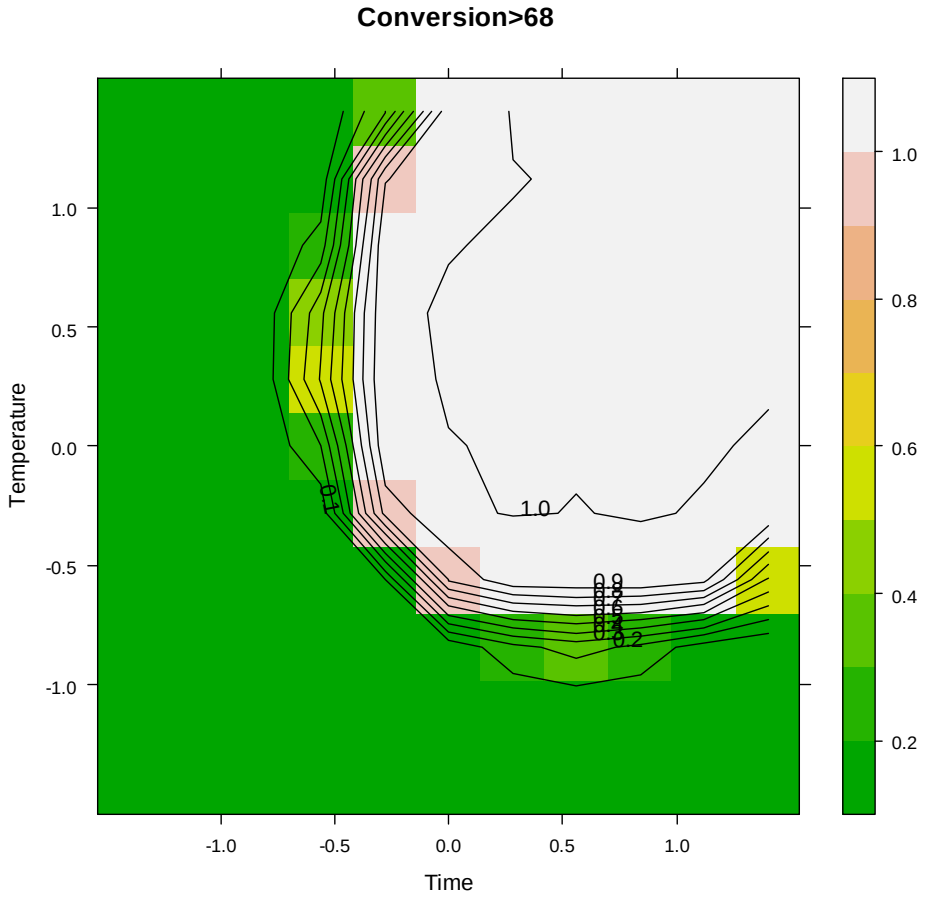
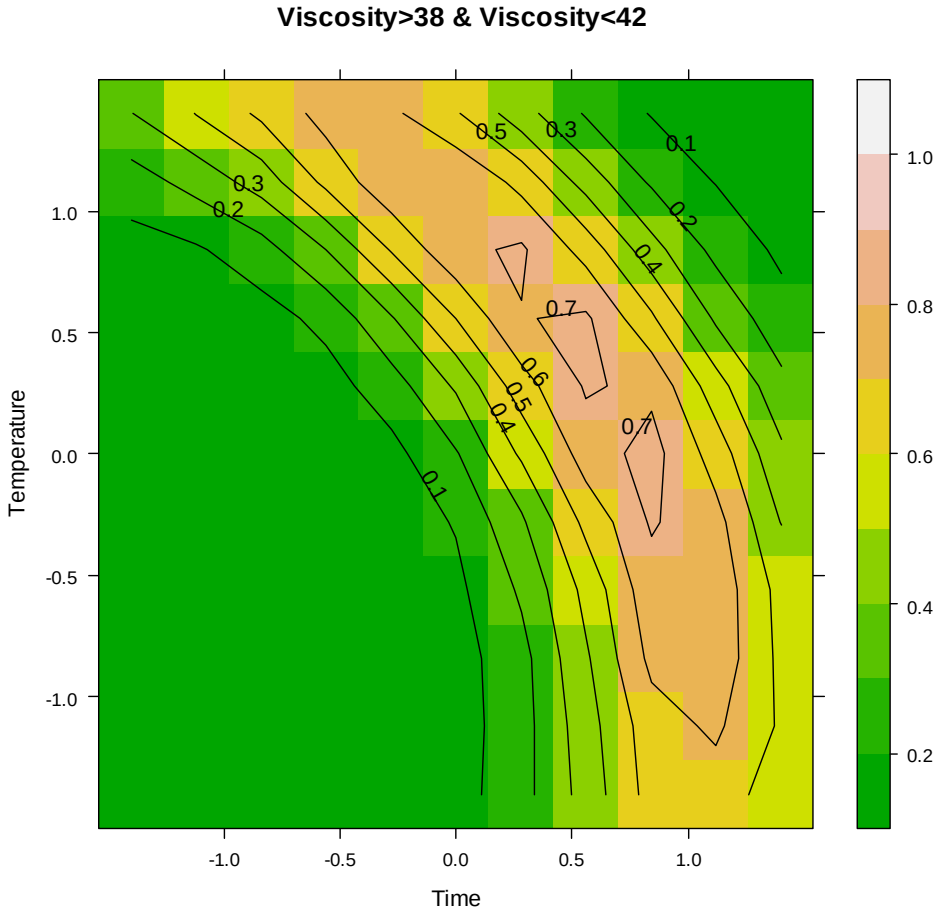
Conversion > 68%



38 < Viscosity < 42



Joint Probability Distribution

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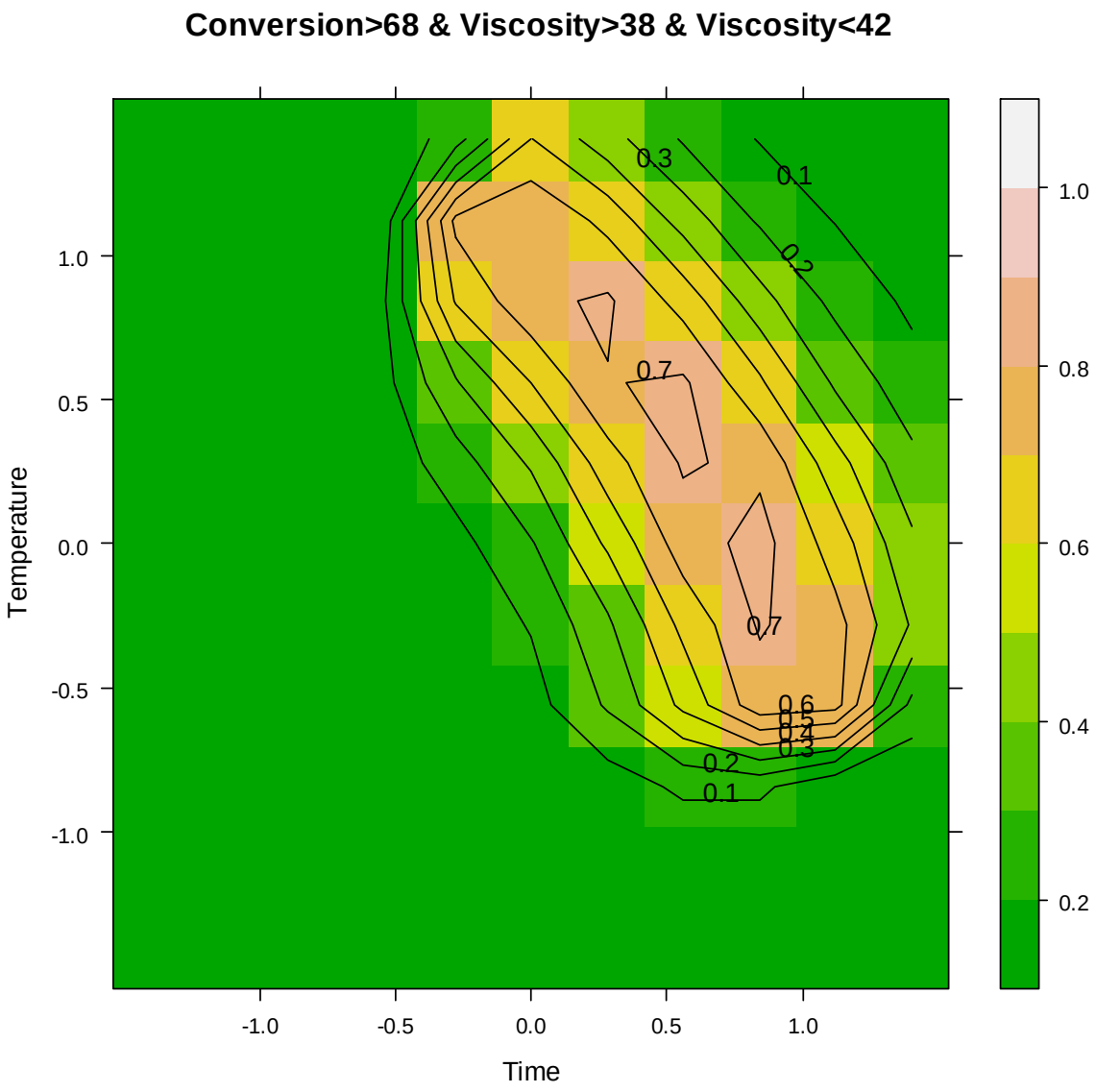
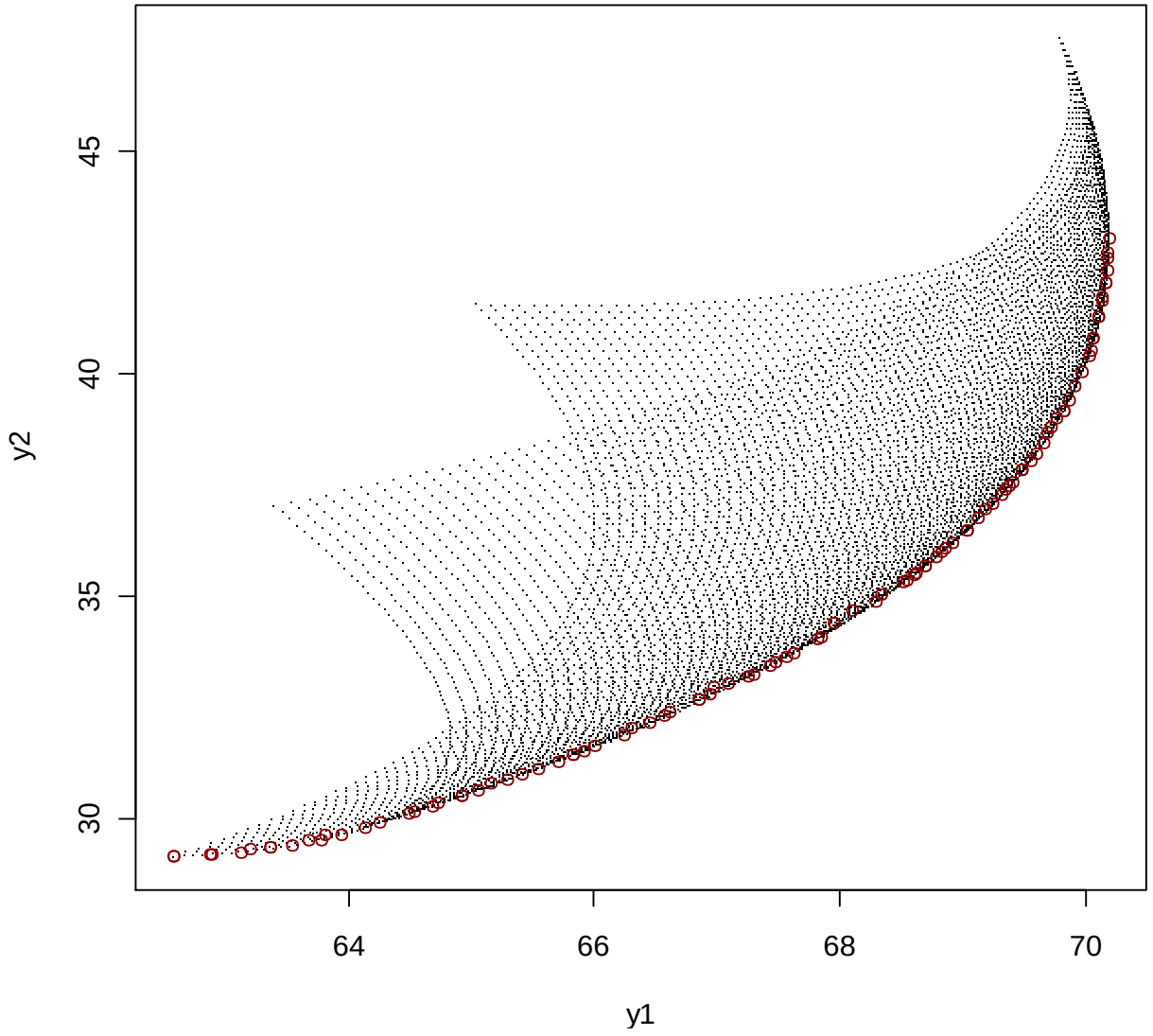
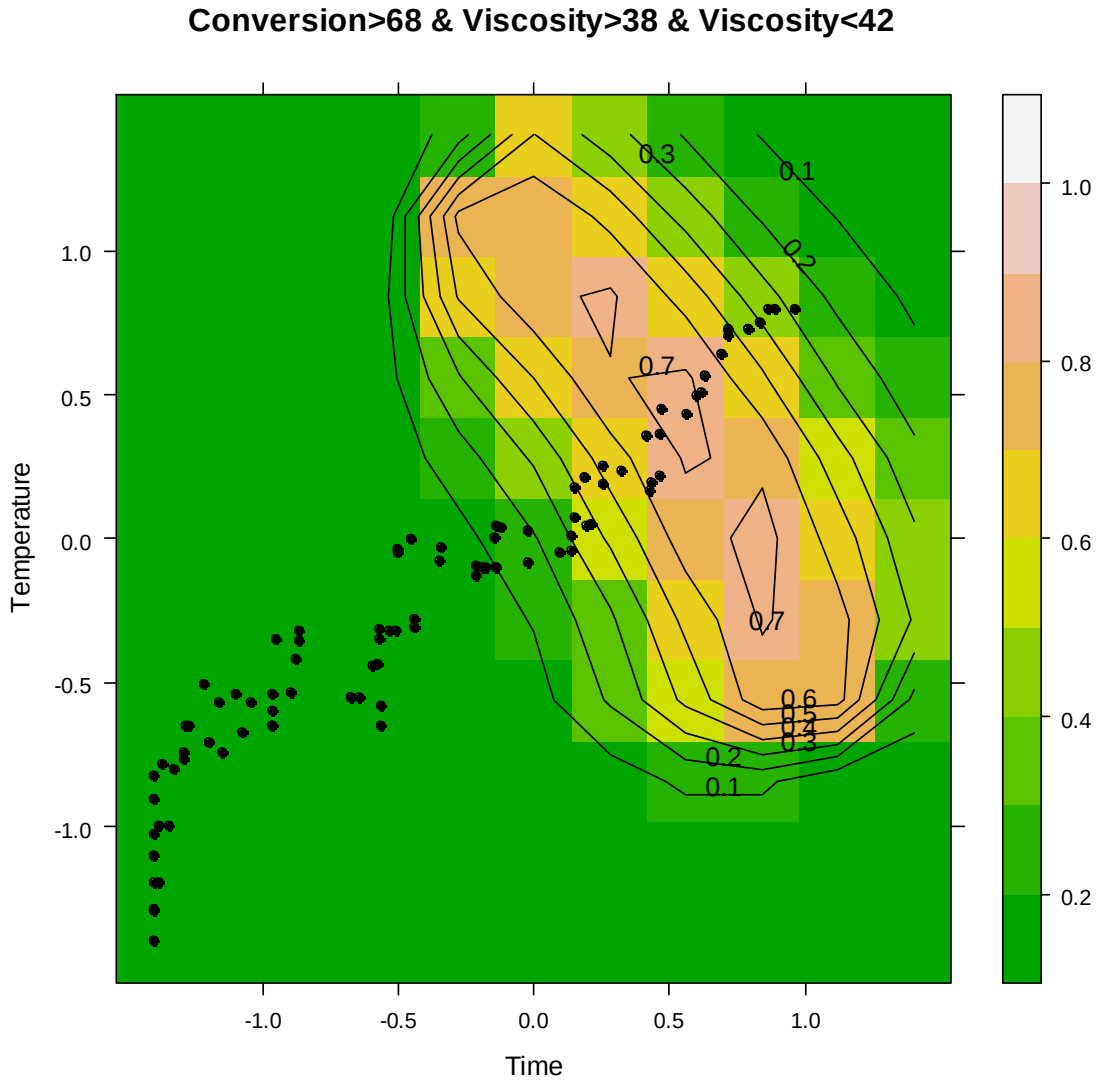


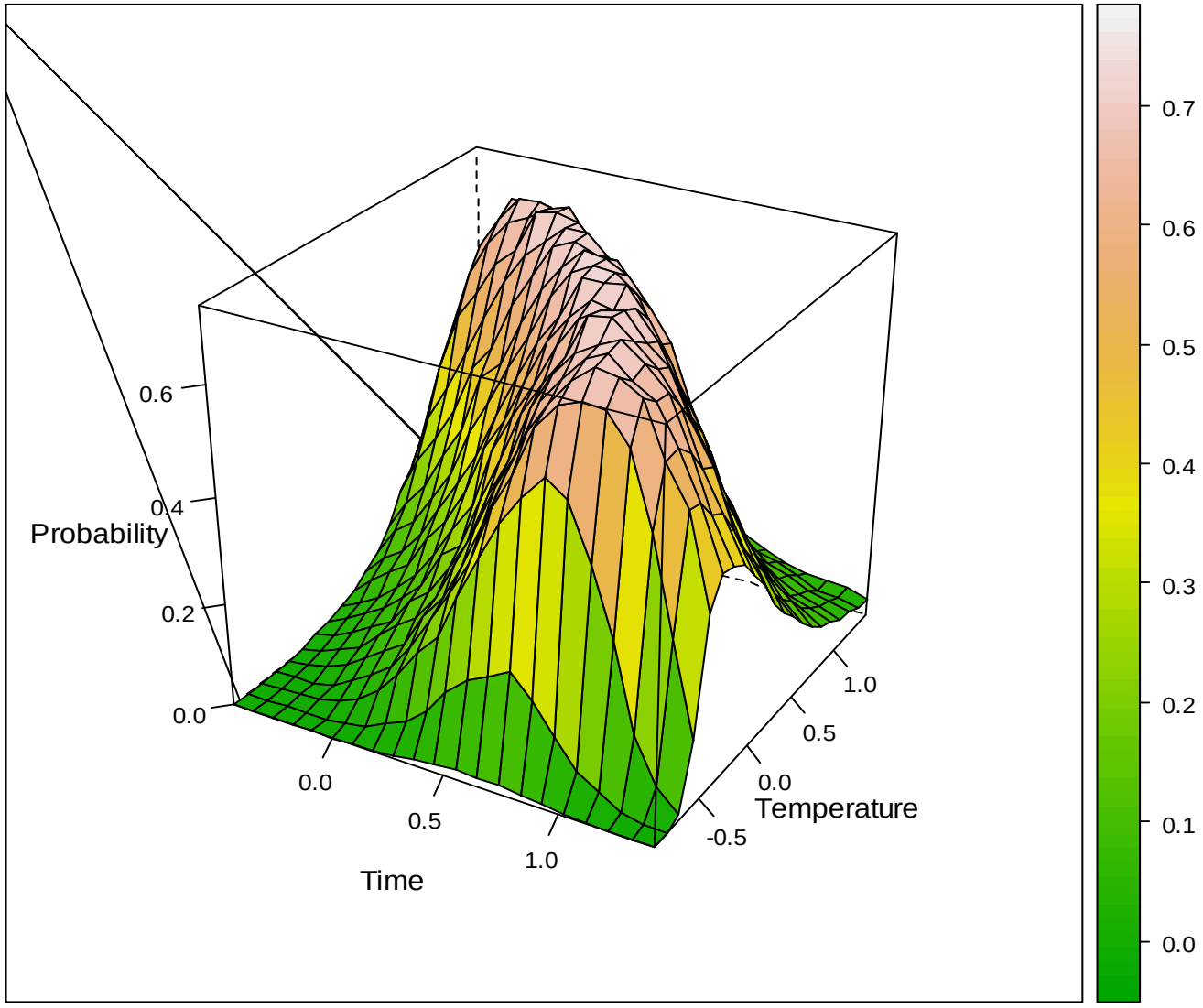
Optimization: Pareto Frontier



Pareto/Joint Probability Overlay



50% Credibility Design Space



take-home message

Benefits of Bayesian Approach

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- Provides estimates of uncertainty in model parameters.
- Enables use of prior information leading to more efficient adaptive design and experimentation.
- Provides a figure of merit (probability) for meeting product profile (specifications) in terms consistent and easy to understand by technical workers operating in a regulated environment.
- Enables use of Pareto optimization in conjunction with risk minimization.
- Enables a means to establish the reliability of the Design Space.
- Provides a basis for selection of alternate process settings within the design space while ensuring "assurance of quality."

References

- John J. Peterson (2004). "A posterior predictive approach to multiple response surface optimization." *Journal of Quality Technology*, 36, 139-153.
- John J. Peterson (2008). "A Bayesian approach to the ICH Q8 Definition of Design Space." *Journal of Biopharmaceutical Statistics*, 18, 959-975.

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