Leveraging Platform Knowledge to Estimate Bioprocess Variability by Applying Bayesian Methodology

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Outline

• Background
• Challenge
• Platform knowledge
• Estimate process variability
• Applications
Challenge: Limited Sample Size
Platform Knowledge

Mab1
- Site1
- Site2
- Site3
- Site4

Mab2
- Site1
- Site2
- Site3
- Site4

Mab3
- Site1
- Site2
- Site3
- Site4

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Different Mean, Similar Variability
Frequentist vs. Bayesian

Frequentist

\[ P(x | \sigma) \]

- \( P(x | \sigma) \) is random
- \( \sigma \) is fixed

Bayesian

\[ P(\sigma | x) \]

- \( \sigma \) is random
- \( P(\sigma | x) \) is fixed
Frequentist Inference
Bayesian Inference

![Graph showing Bayesian Inference with a normal distribution curve]
CQA $y_i \sim N(\mu_i, \sigma)$

$\mu_i = \mu_0 + \alpha_{a_i} + \beta_{b_i}$

Overall Mean $\mu_0 \sim uniform(0,100)$

Molecule Effect $\alpha_{a_i} \sim N(0,100)$

Location Effect $\beta_{b_i} \sim N(0,100)$

Process Variability $\sigma \sim uniform(0,5)$
## Platform Process Variability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>2.5%</th>
<th>Median</th>
<th>97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Variance</td>
<td>0.244</td>
<td>0.033</td>
<td>0.188</td>
<td>0.242</td>
<td>0.319</td>
</tr>
</tbody>
</table>
Update Prior Information

Probability

X
## Limited Data From One New Molecule

<table>
<thead>
<tr>
<th>Scale (L)</th>
<th>CQA</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000</td>
<td>96.70</td>
</tr>
<tr>
<td>5000</td>
<td>96.71</td>
</tr>
<tr>
<td>5000</td>
<td>97.45</td>
</tr>
<tr>
<td>Mean</td>
<td>96.95</td>
</tr>
<tr>
<td>SD</td>
<td>0.43</td>
</tr>
</tbody>
</table>

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Conjugated Prior for Variance

$Y \sim N(\mu, \sigma^2)$

If $\sigma^2 \sim IG(\alpha, \beta)$

Then $\sigma^2 \sim IG \left( \alpha + \frac{n}{2}, \beta + \frac{\sum(y_i - \mu)^2}{2} \right)$
Estimate $\alpha$ and $\beta$

$X \sim \text{inverse gamma}(\text{shape } \alpha, \text{scale } \beta)$

$$f(x) = \frac{\beta^\alpha}{\Gamma(\alpha)} x^{-\alpha - 1} \exp\left(-\frac{\beta}{x}\right)$$

$$E(X) = \frac{\beta}{\alpha - 1}$$

$$\operatorname{Var}(X) = \frac{\beta^2}{(\alpha - 1)^2(\alpha - 2)}$$

$$\alpha = \frac{[E(x)]^2}{\operatorname{Var}(X)} + 2$$

$$\beta = E(X)(\alpha - 1)$$
Prior distribution $\sigma^2 \sim IG(56.46, 13.56)$
Posterior distribution $\sigma^2 \sim IG(57.96, 13.65)$
95% confidence interval for $\sigma^2$: [0.057, 7.51]
Process standard deviation $\sigma = 0.5$
Potential Applications

- Parameter classification
- Scale down model qualification
- Risk assessment
- DOE acceptance criteria
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