A Comparison between Frequentist vs. Bayesian in Stability Data Analysis

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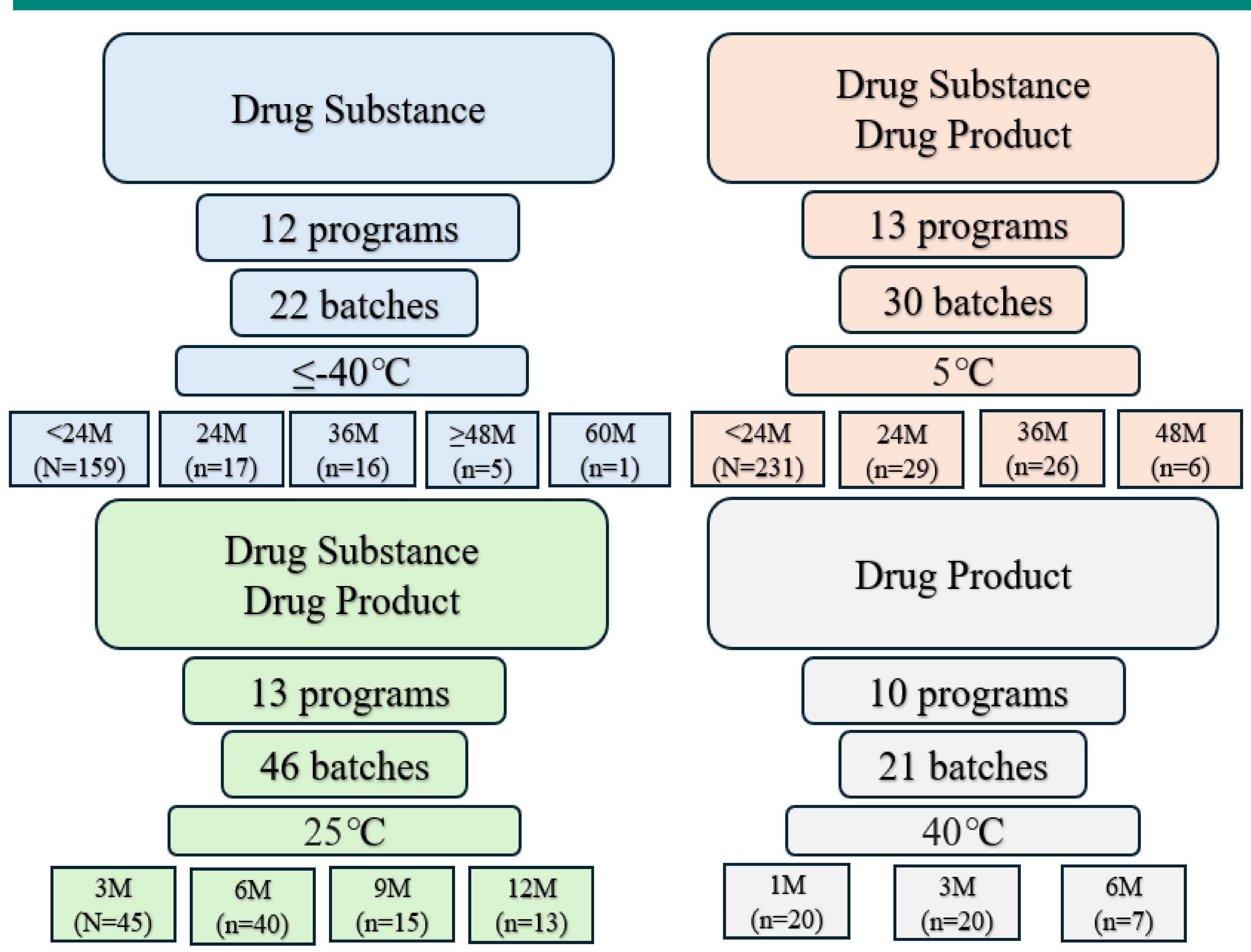
Introduction

Understanding the stability of a pharmaceutical product is crucial for quality design throughout its product life cycle, which remains a significant challenge. The frequentist approach for predicting statistical stability for a given attribute involves multiple steps, such as modeling Drug Substance (DS) and Drug Product (DP) data separately and fitting a common slope model. This study introduces a Bayesian separate intercept and separate slope (SISS) model procedure to predict values for future batches. Using a sufficient number of product batches, we demonstrate that the Bayesian approach yields results comparable to the frequentist approach.

Prior knowledge

- Internal knowledge: *from development and manufacturing (ackn: Geetha Thiagarajan)*
- External knowledge: *Scientific and technical publications (including literature and peer reviewed publications)*
- Established scientific principles: *Common (textbook) knowledge*
- ***Bayesian method/modeling***

Data



Statistical Methods

Frequentist Approach:

Step 1:

- Compute 95%/99% tolerance interval (TI) based on DS release and stability data (TI is 3%).

Step 2:

- Slope estimates from DS and DP batches that have >6M stability data at 5ºC.
- The starting point of all batches are set to 3.0 (worst case). Fit a linear model with separate slope model.

Bayesian Approach: <u>SISS Model</u>

Step1: DS data

$$Y_i \sim N(\mu_i, \sigma^2)$$
$$\mu_i = \beta_0 + L_i + (\beta_1 + B_i) \times t$$

Prior:

$$\beta_0 \sim N(a_0, \tau_0);\ \beta_1 \sim N(a_1, \tau_1);$$
$$a_0 \sim N(0,100);\ a_1 \sim N(0,100);$$
$$\sigma_0 \sim U(0,100);\ \sigma_1 \sim U(0,100);$$
$$\tau_0 = 1/\sigma_0^2;\ \tau_1 = 1/\sigma_1^2$$

Step 2: *DS/DP with more than 6M. Fit SISS model, assuming prior for β_0 based on Step 1 DS data analysis. Compute predictive distribution and 95% Credible Interval for future batch.*

<u>King-Kung-Fung Model (KKF)</u>

$$Y_i \sim N(\mu_i, \sigma^2)$$
$$\mu_i = \alpha_{b[i]} - k_{b[i]} \cdot exp\left(\frac{E_a}{R}\left(\frac{1}{T_{ref}} - \frac{1}{T}\right)\right) \cdot t$$

- $\alpha_{b[i]}$ = batch specific intercept
- $k_{b[i]}$ = batch specific rate constant at T_{ref}
- R = universal gas constant, E_a activation energy
- Arrhenius Equation $\quad k = A \cdot exp\left(-\frac{E_a}{RT}\right)$

Hierarchical Priors:

$$\alpha_{b[i]} \sim N(3,1);\ k_{b[i]} \sim N(k_{ref}, \sigma_k);$$
$$E_a^* \sim N(20,1);\ k_{ref} \sim TN(0.5, 5)$$
$$\sigma \sim U(0,100);\ \sigma_k \sim U(0,100);$$

***Sensitivity analyses were conducted, and prior choice did not impact the results significantly.**

Results

Figure 1. Results of Prediction with 95% Credible Intervals – SISS Model.

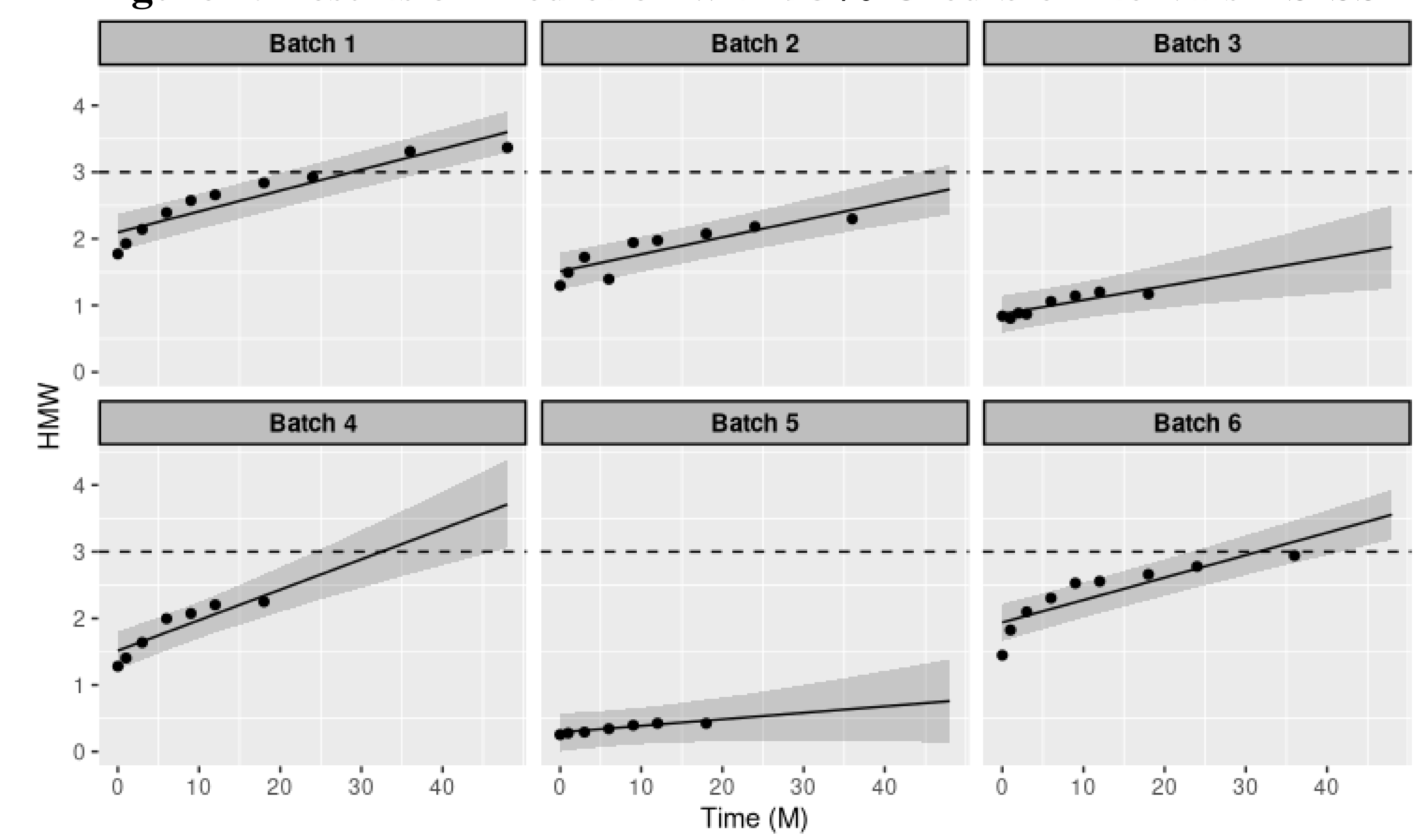
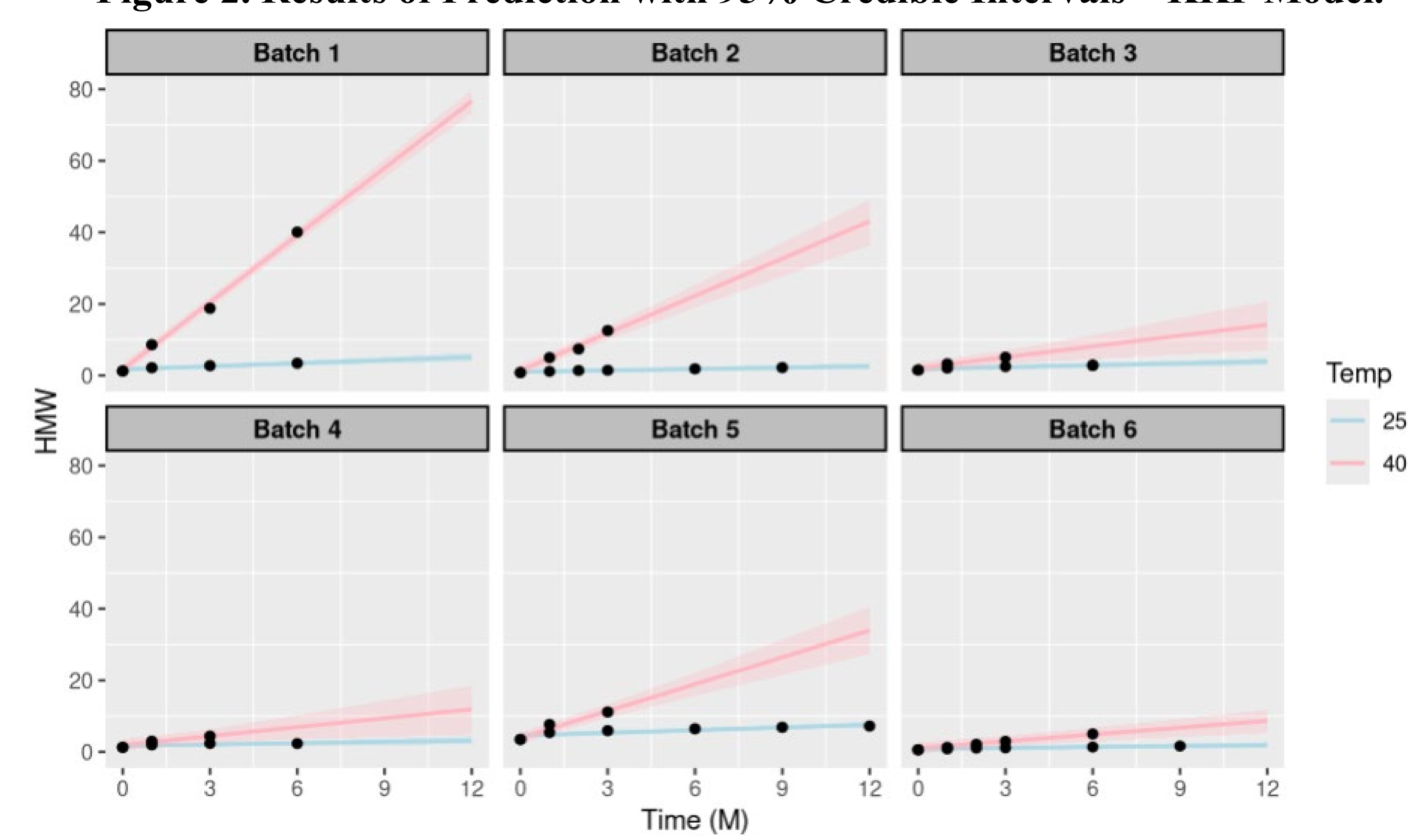


Table 1. Results of Rate of Change (worst case slope) between Models.

Model	6 months	12 months	24 months
Frequentist approach	0.25	0.50	1.01
SISS model	0.28	0.55	1.10
KKF model	0.31	0.61	1.12

Figure 2. Results of Prediction with 95% Credible Intervals – KKF Model.



Conclusion and Discussion

Bayesian approaches produce results comparable to the frequentist approach. Future step should consider incorporating non-linearities to capture the data at different conditions.