Using a Bayesian strategy to predict attribute values at shelf life

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Outline

- Short description of the problem
- Some notes on Bayesian analyses versus Frequentist analyses
- Application to the data
- Storage data at 2 temperatures versus 1 temperature
- Conclusions

The problem

- Current manufacturing site has lots of experience in producing a monoclonal antibody
- Many batches had been produced, and long-term stability studies have been performed

- New manufacturing site is qualified
- Few batches will be produced
- Time allows only short-term stability studies
- **Extensive chemical characterization will be done, to demonstrate comparability of material with current site**

- Based on few stability data, and assuming comparability, what can be claimed concerning shelf life in terms of predicted attribute values after 36 months at 5°C?

The problem

- Current guideline indicates performing linear regression over available data, with extrapolation

- Extrapolation can lead to very wide confidence intervals

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

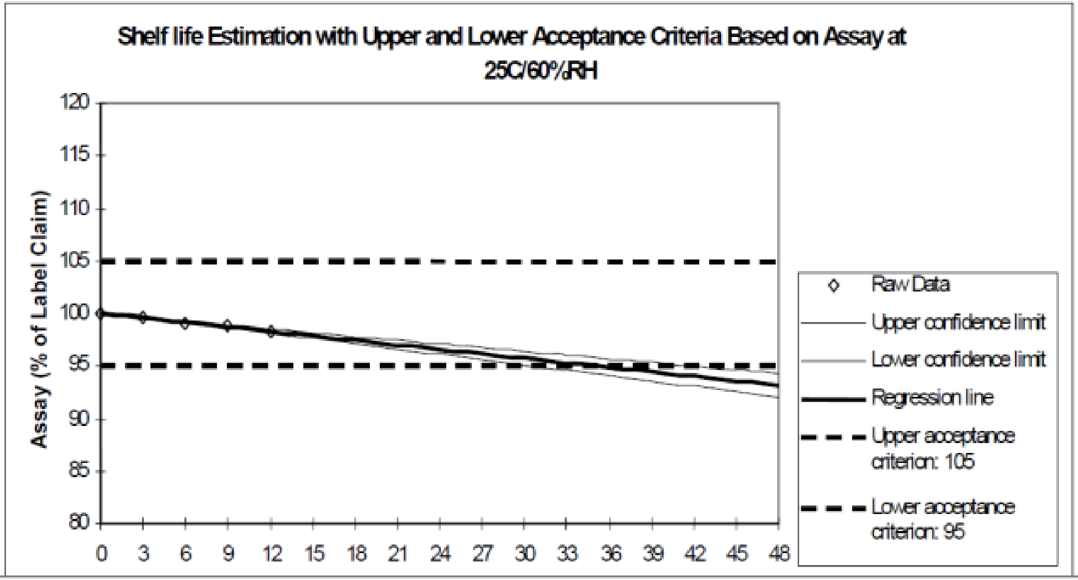
EVALUATION FOR STABILITY DATA

Q1E

Evaluation of Stability Data

B.7 Figures

Figure 1



Towards a solution

- Current manufacturing site has lots of experience in producing a monoclonal antibody
- Many batches had been produced, and long-term stability studies have been performed

- New manufacturing site is qualified
- Few batches will be produced
- Time allows only short-term stability studies
- Extensive chemical characterization will be done, to demonstrate comparability of material with current site

- Can the knowledge obtained in the current manufacturing site be used as prior knowledge to analyze the data of the new site?
- As there are no data from the new site yet, perform a study using data from the current site

Using prior knowledge: Bayesian statistics

Two types of statistical strategies:

- Frequentist statistics
- Bayesian statistics

Frequentist statistics

- Start with a null-hypothesis concerning the true population value of the relevant parameter (can be more than one parameter)
- Given this hypothesis, construct the probability distribution of the observable result
- Based on this distribution, define which results can be considered 'likely' or 'reasonable' and which results are not
  'reasonable' is typically defined in terms of a frequency of 95%
- Perform the experiment and see where you end up

Frequentist statistics

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- Perform the experiment and see where you end up

- All inferences are based on the probability of observing the actual result given the hypothesized value (referred to as ‘the likelihood’)
  Probability(data given fixed population parameters)
- Results are typically expressed as point estimates with confidence intervals
- Only the data of the current experiment are used

Bayesian statistics

- Start with asking yourself: what do we already know (prior knowledge)
- The prior knowledge comes with uncertainty, and is captured in a probability distribution
- Goal of the experiment is to update the knowledge on the relevant parameters with new information that comes from the experiment

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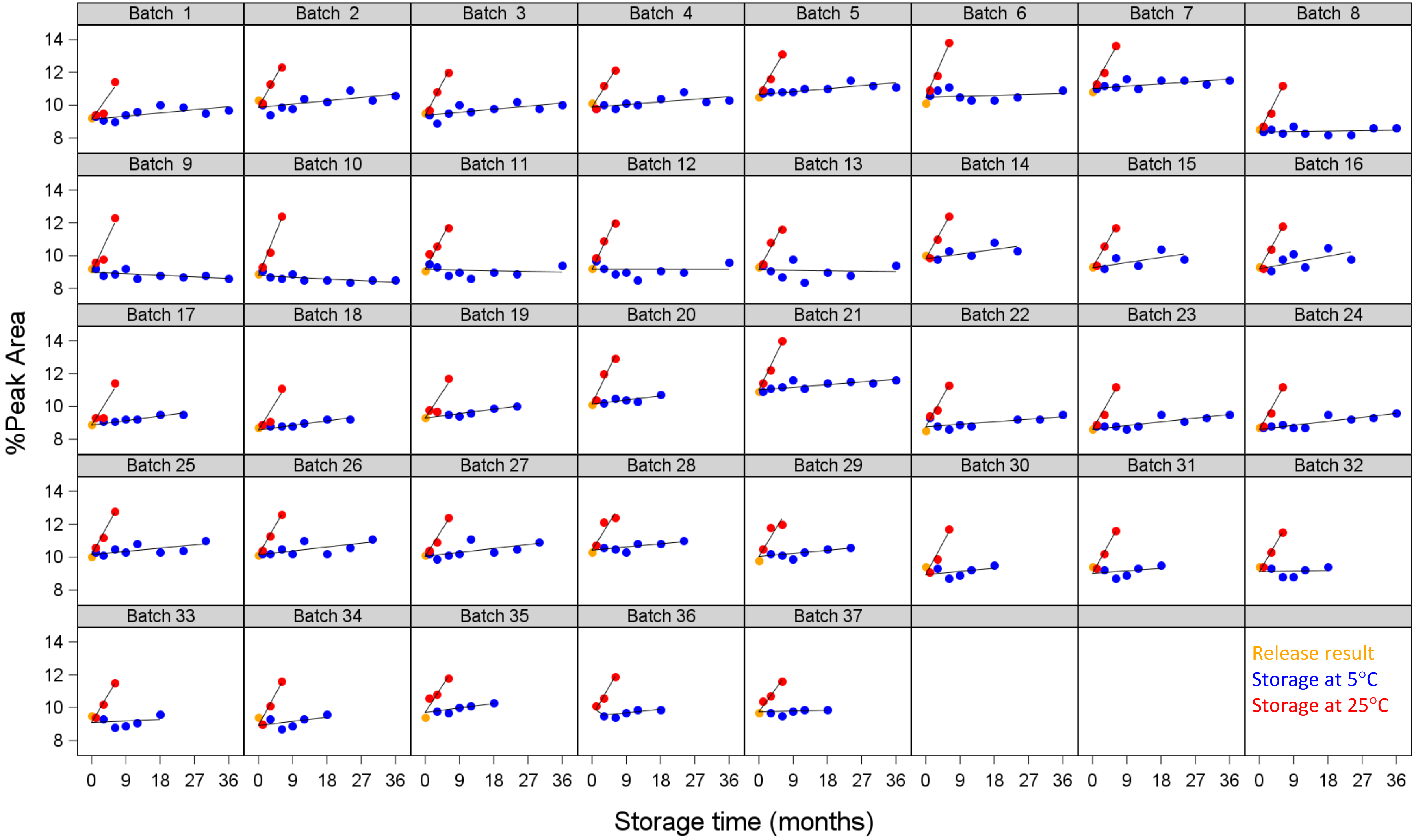
- Perform the experiment
- Combine the results of the experiment (the likelihood) with the prior knowledge to obtain the posterior distribution
- All inferences are based on the posterior distribution of the parameters
  Probability(population parameters given fixed data)
- Results are typically expressed in terms of distributions, reflecting the knowledge on the parameters

The problem

- There is lot of knowledge in the data from the current site
- Can we include this knowledge in the analysis of the data of the new site?
- We need a Bayesian strategy

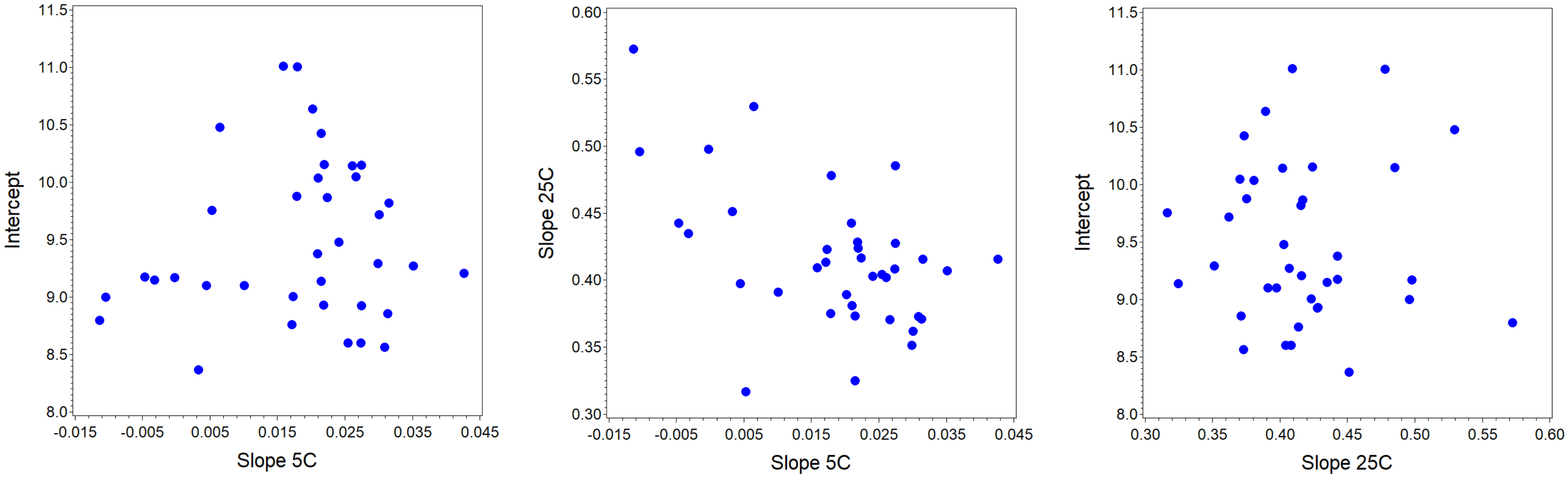
Historic data

- Current site: 37 batches stored at 5°C up to 36 months and at 25°C up to 6 months



The prior knowledge concerning the regression parameters

- For every historic batch, we can perform linear regression with 3 parameters: one intercept (α), two slopes (β_5 and β_{25})
  - $Y = \alpha + \beta_5$*time for results at 5°C
  - $Y = \alpha + \beta_{25}$*time for results at 25°C
- Assume the observed regression parameters are realizations from a three-dimensional normal distribution, with a mean vector and covariance matrix



The analysis

- Initial interest focuses on the regression parameters
- Based on the posterior knowledge in the regression parameters, the predicted response after 36 months at 5°C can be calculated

- Bayesian (*theorem attributed to Thomas Bayes, 1701(?)-1761*):

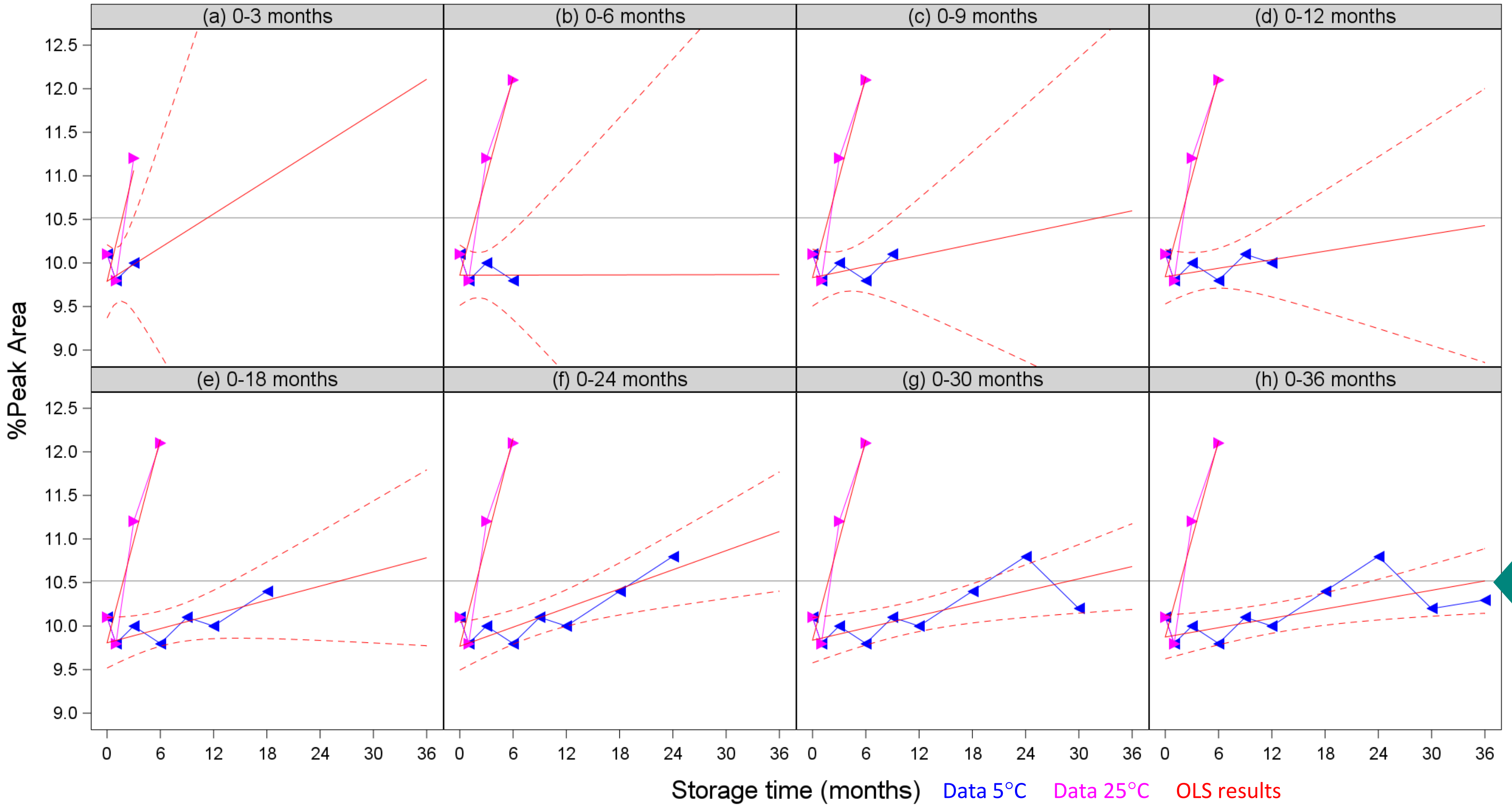
$$\underbrace{Pr(parameters \mid data)}_{\text{Posterior}} \propto \underbrace{Pr(data \mid parameters)}_{\text{Likelihood}} * \underbrace{Pr(parameters)}_{\text{Prior}}$$

Prior → Three-dimensional distribution of regression parameters (mean vector and covariance matrix)

- With few data from the new batch, the prior dominates the result
- With many data from the new batch, the data dominates the result

Frequentist analysis

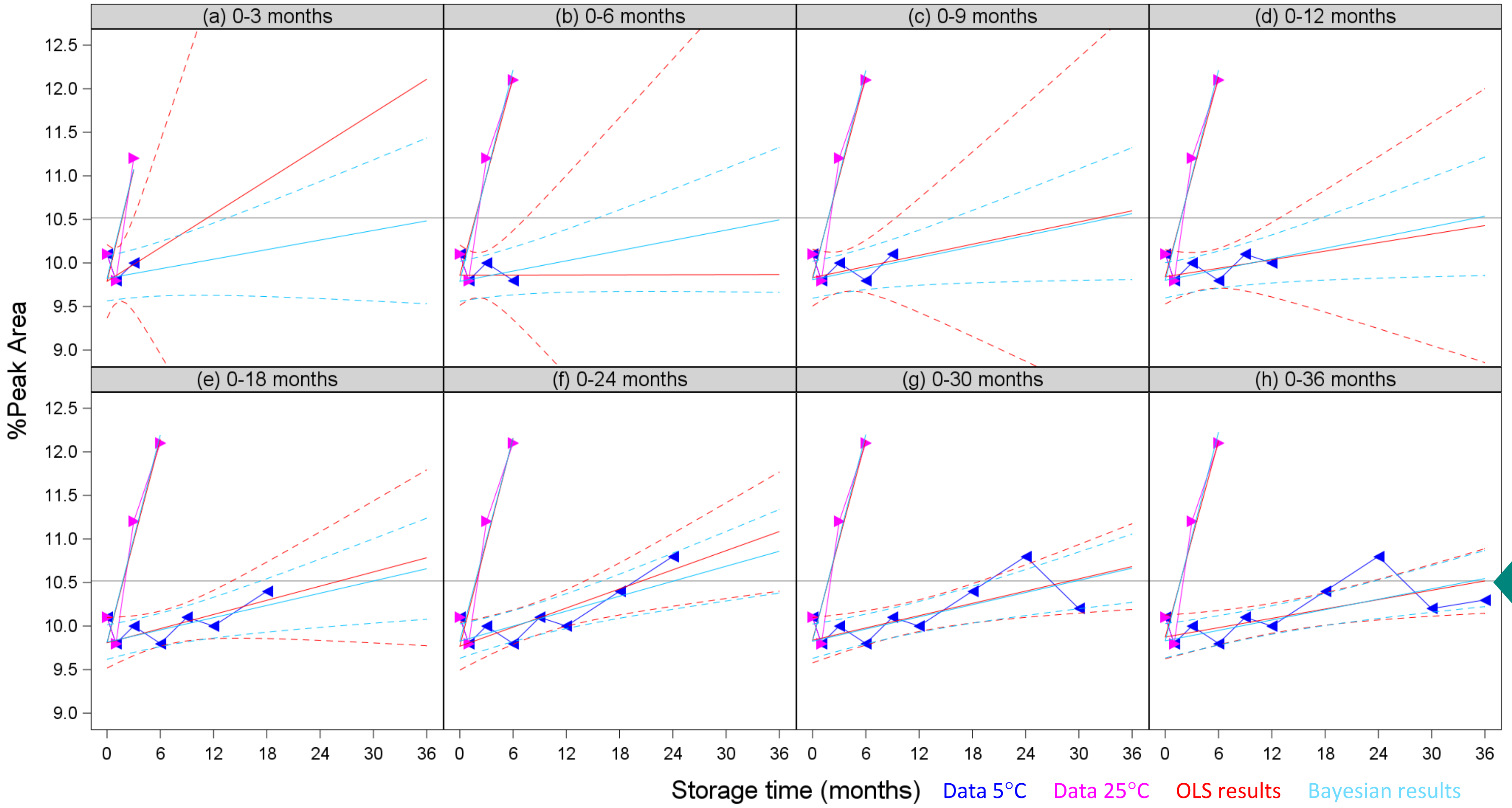
- Take one batch and analyze the data using ordinary least squares (OLS) while continuously adding extra data



Reference line indicates predicted result using all data

Frequentist versus Bayesian analysis

- Take one batch and analyze the data using both strategies while continuously adding extra data



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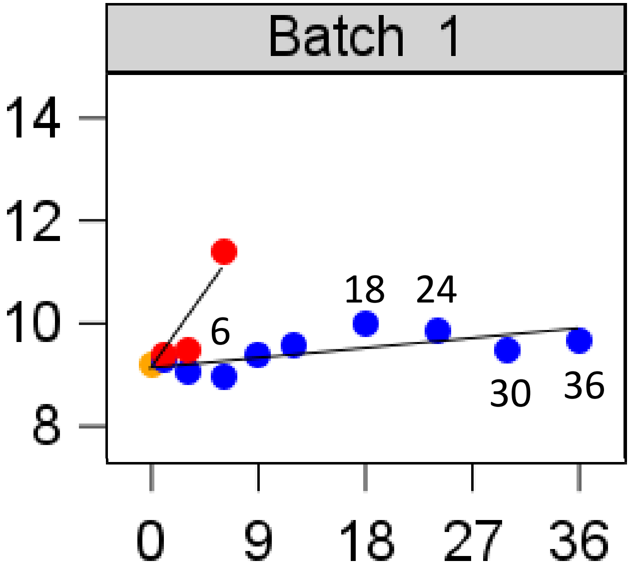
Frequentist versus Bayesian analysis – predictions with extrapolation

Predict response at 36 months based on:

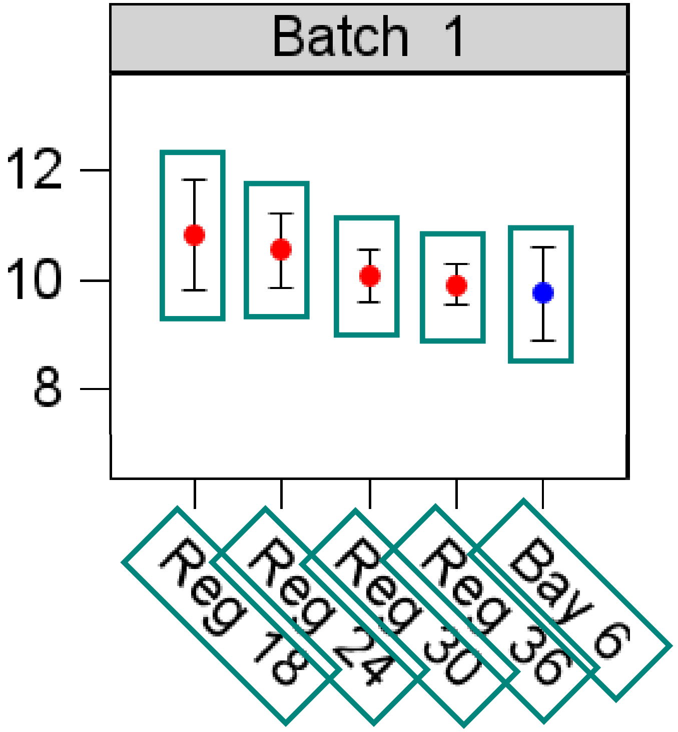
- OLS using 18 months of data
- OLS using 24 months of data
- OLS using 30 months of data
- OLS using 36 months of data
- Bayes using 6 months of data

Error bars reflect 95% confidence / credible intervals

Complete data set
with OLS lines up to 36M



Predictions for 36 months
with 95% interval



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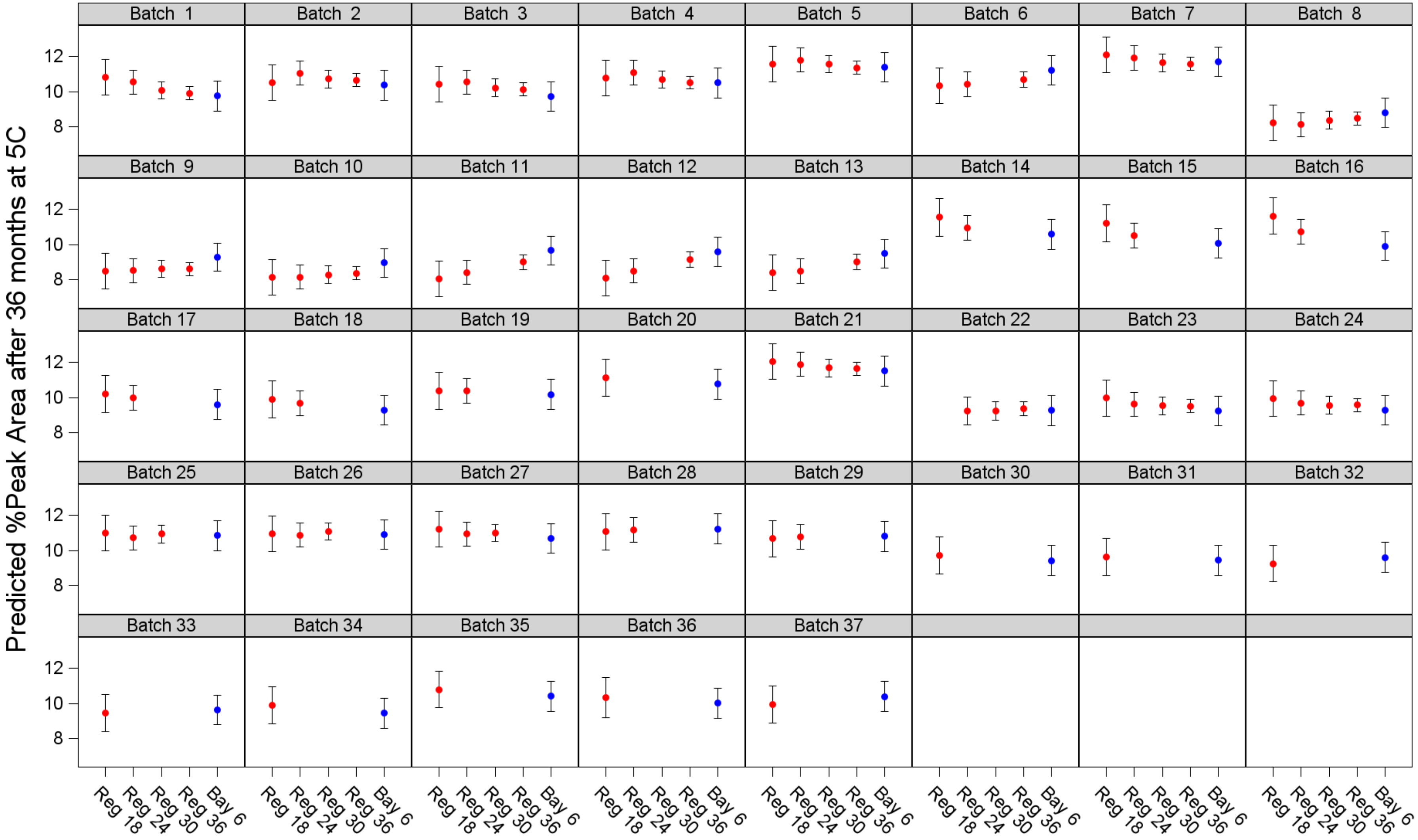
Not all batches contribute with data exceeding 18 months

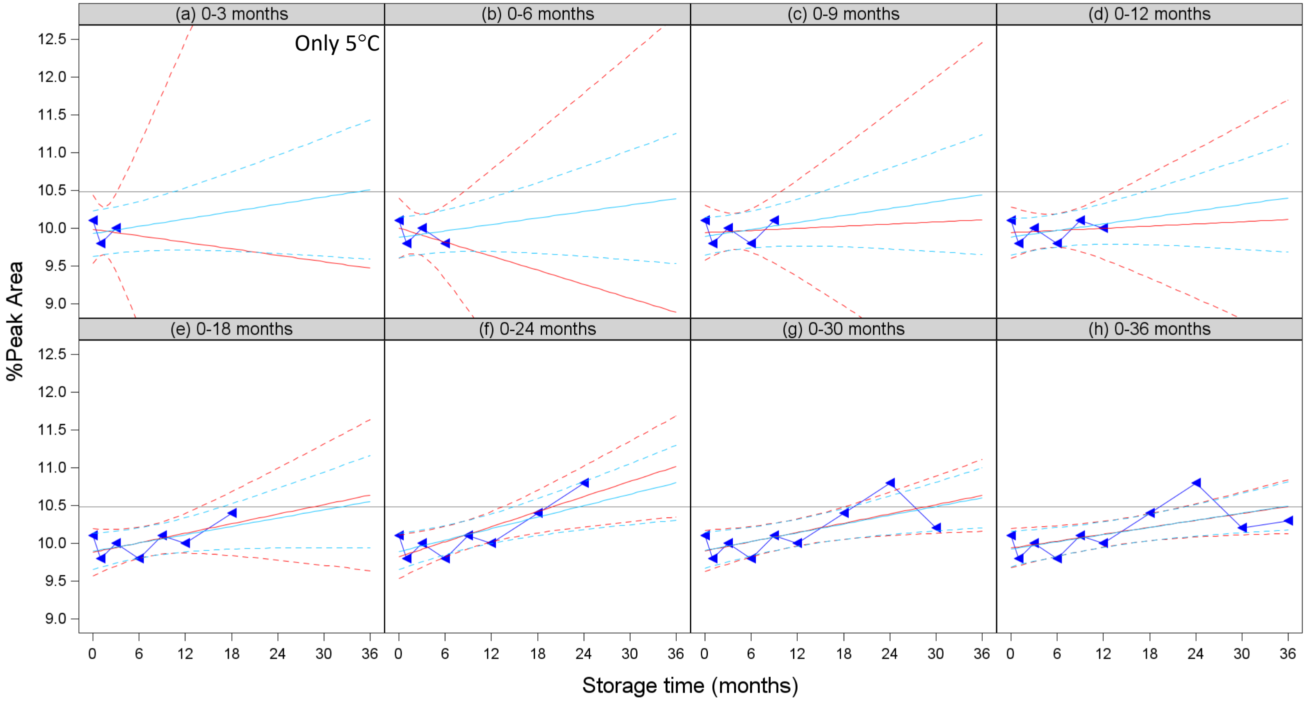


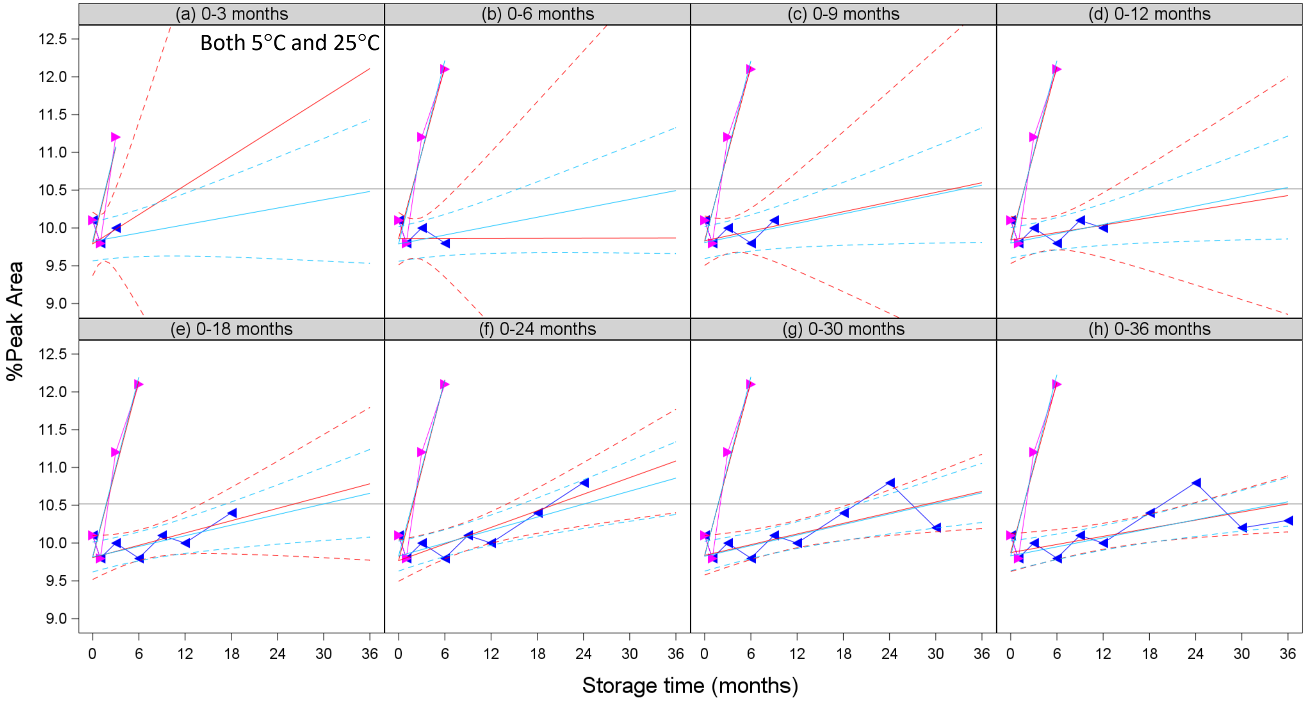
Multiple temperatures

- Same strategy can be used using only data at 5°C

- Change over short term at 5°C is in the order of analytical noise
- Change over short term at 25°C exceeds the order of analytical noise
- Using data from both temperatures leads to a better estimate of the intercept and hence of the slope at 5°C

- Using data from both temperatures can add to the power





Conclusions

- Extensive extrapolation from short-term stability data can yield confidence intervals that are too wide for practical use
- Under the assumption of comparability, effective use can be made of historic data using a Bayesian strategy
- One can choose to include stability data observed at a single storage condition or multiple storage conditions
- Bayesian predictions for 36 months based on 6 months of stability data are well in line with the results observed after prolonged storage