Bayesian Statistics: Using Prior Knowledge to Enhance Understanding of Product-Specific Stability

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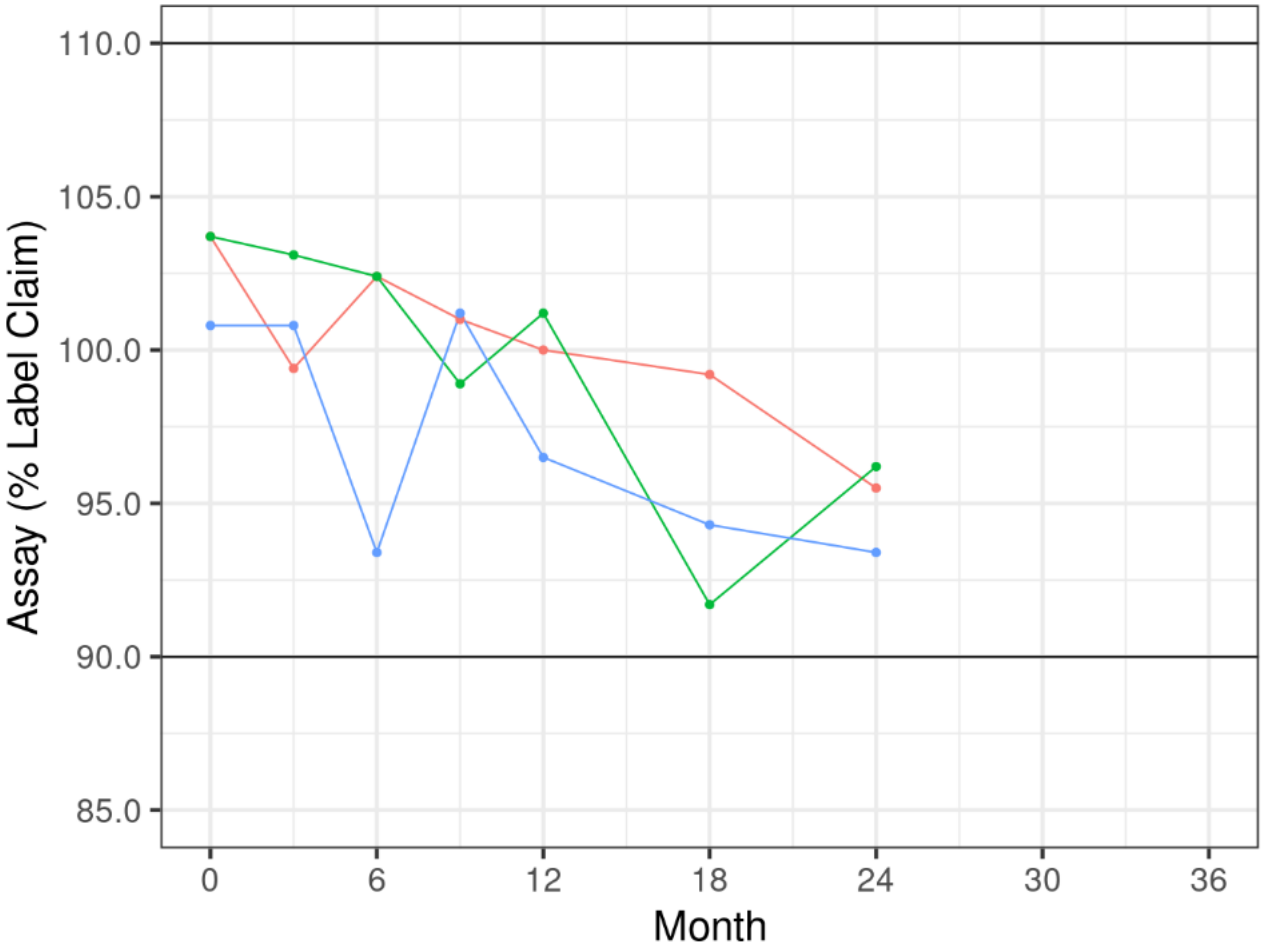
Product Stability



- 3 batches with 24 months stability data
- Specification acceptance criteria 90.0-110.0% Assay (% Label Claim)
- What is the shelf-life?

Outline

What is Bayesian statistics?

Bayesian approach to modeling stability data

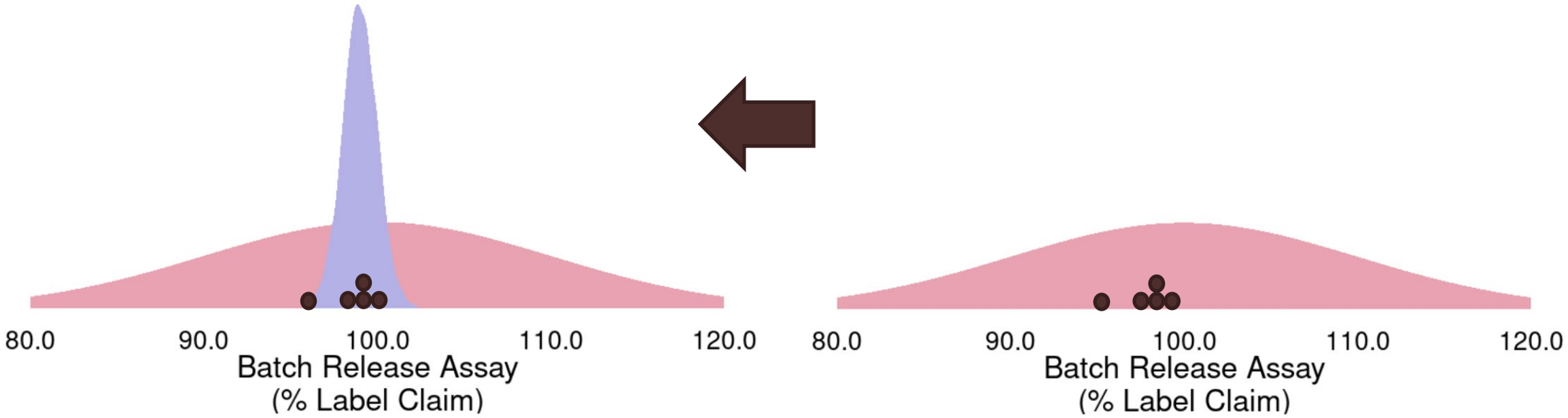
Approaches to utilizing prior knowledge

Bayesian Inference

$$Prob(\text{unknown parameters}|\text{data}) \propto Prob(\text{data}) \times Prob(\text{unknown parameters})$$

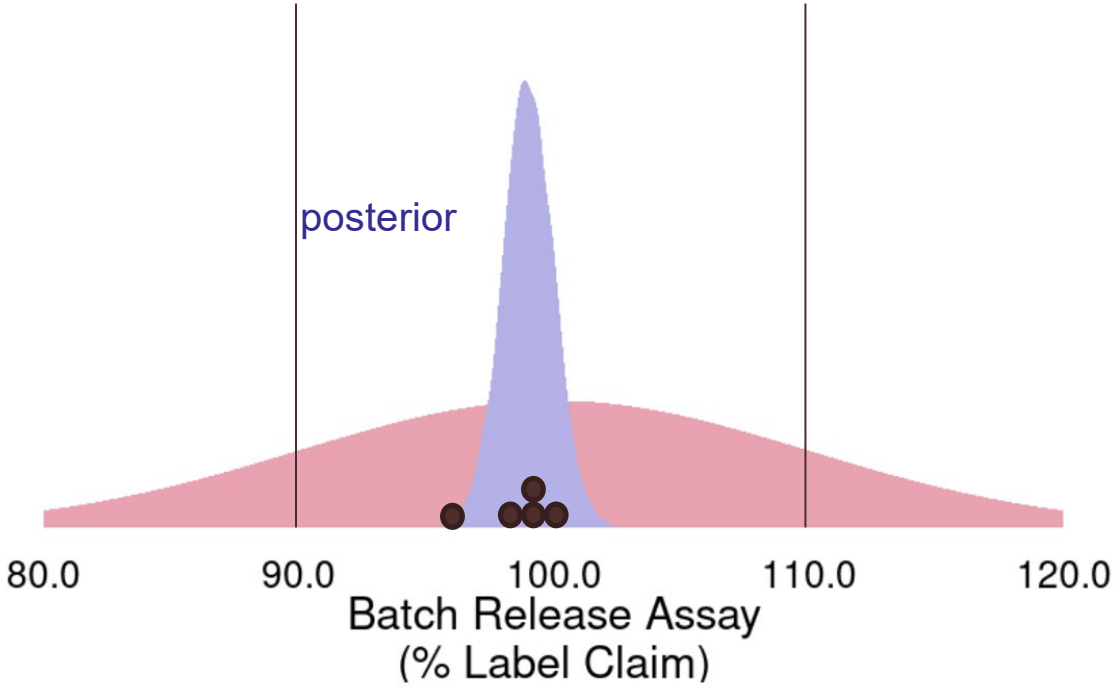
Posterior distribution

Prior distribution

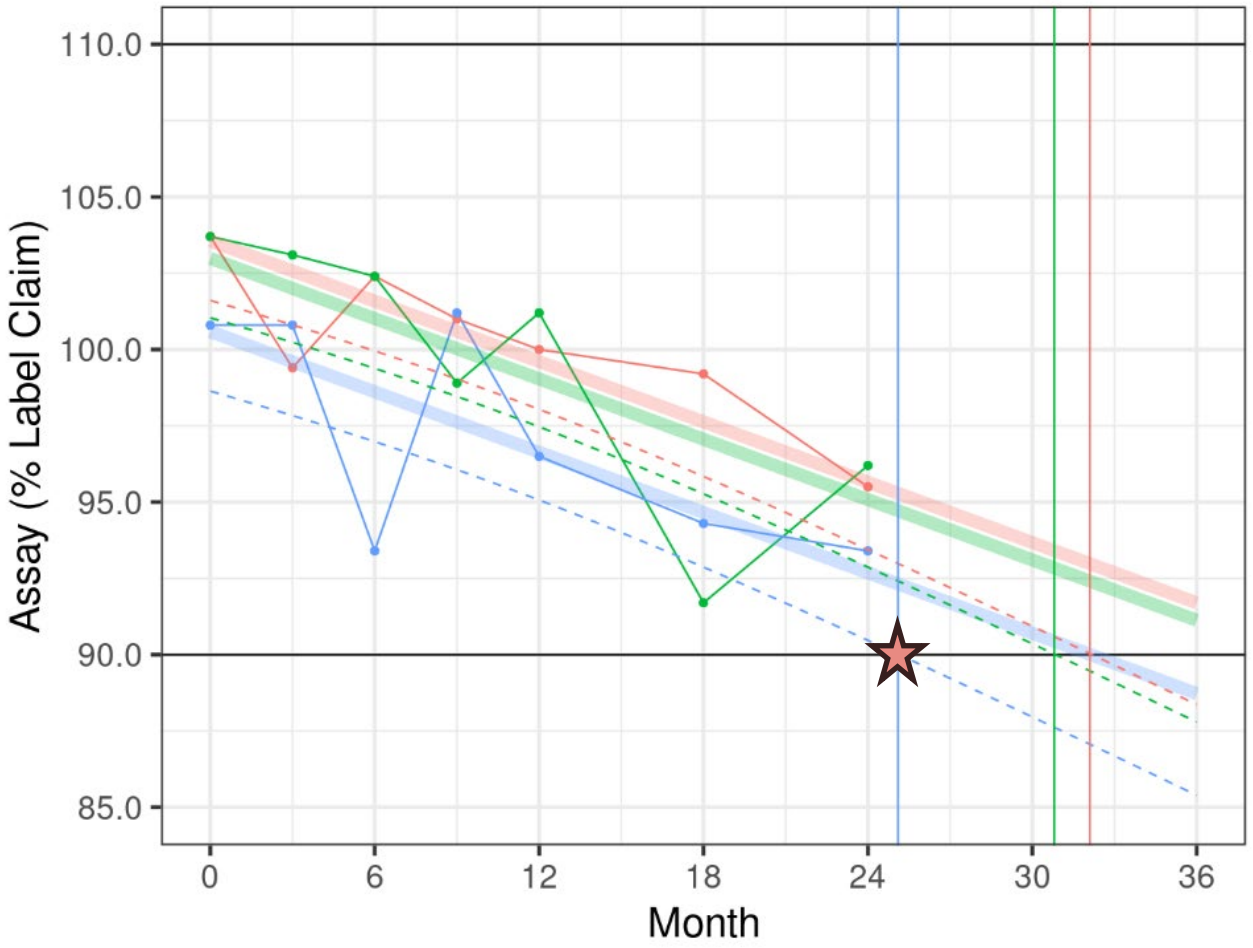


Bayesian Inference

- All inference is based on the posterior distribution
- Can answer questions using **probabilistic conclusions**
  - What is the probability that Assay (% Label Claim) at batch release is within 90.0-110.0?



Shelf-life determination – ICH Q1E

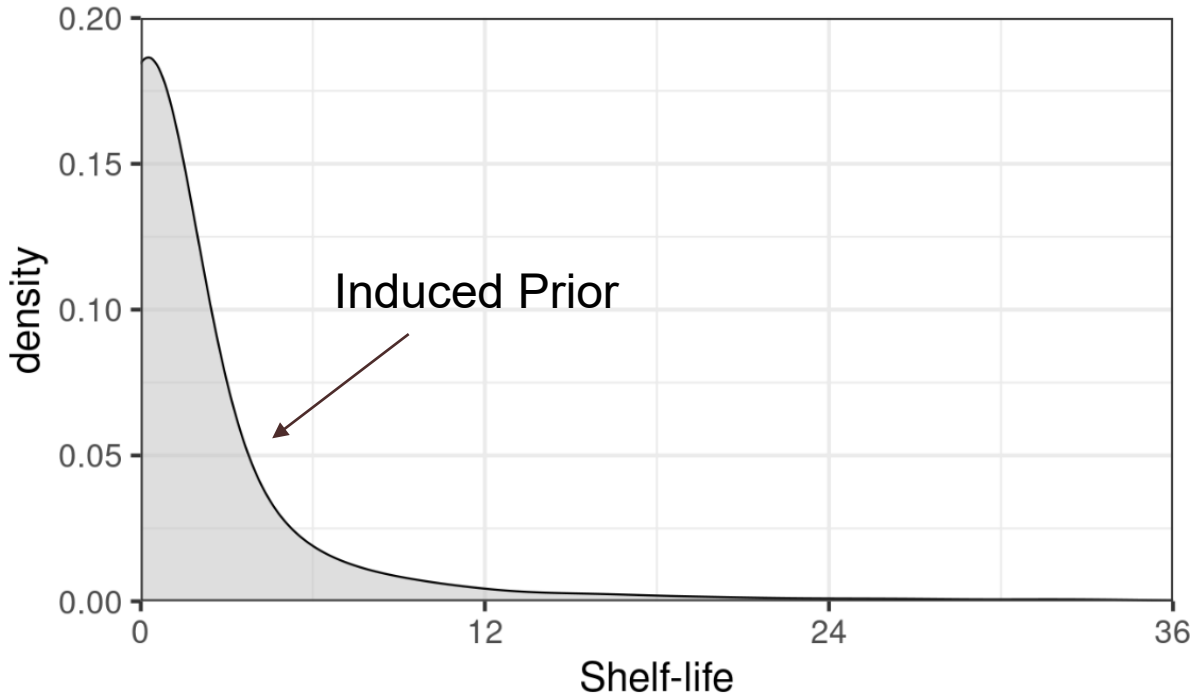


- Batches share a common slope
- 95% confidence limits
- Shelf-life = 25.1 months

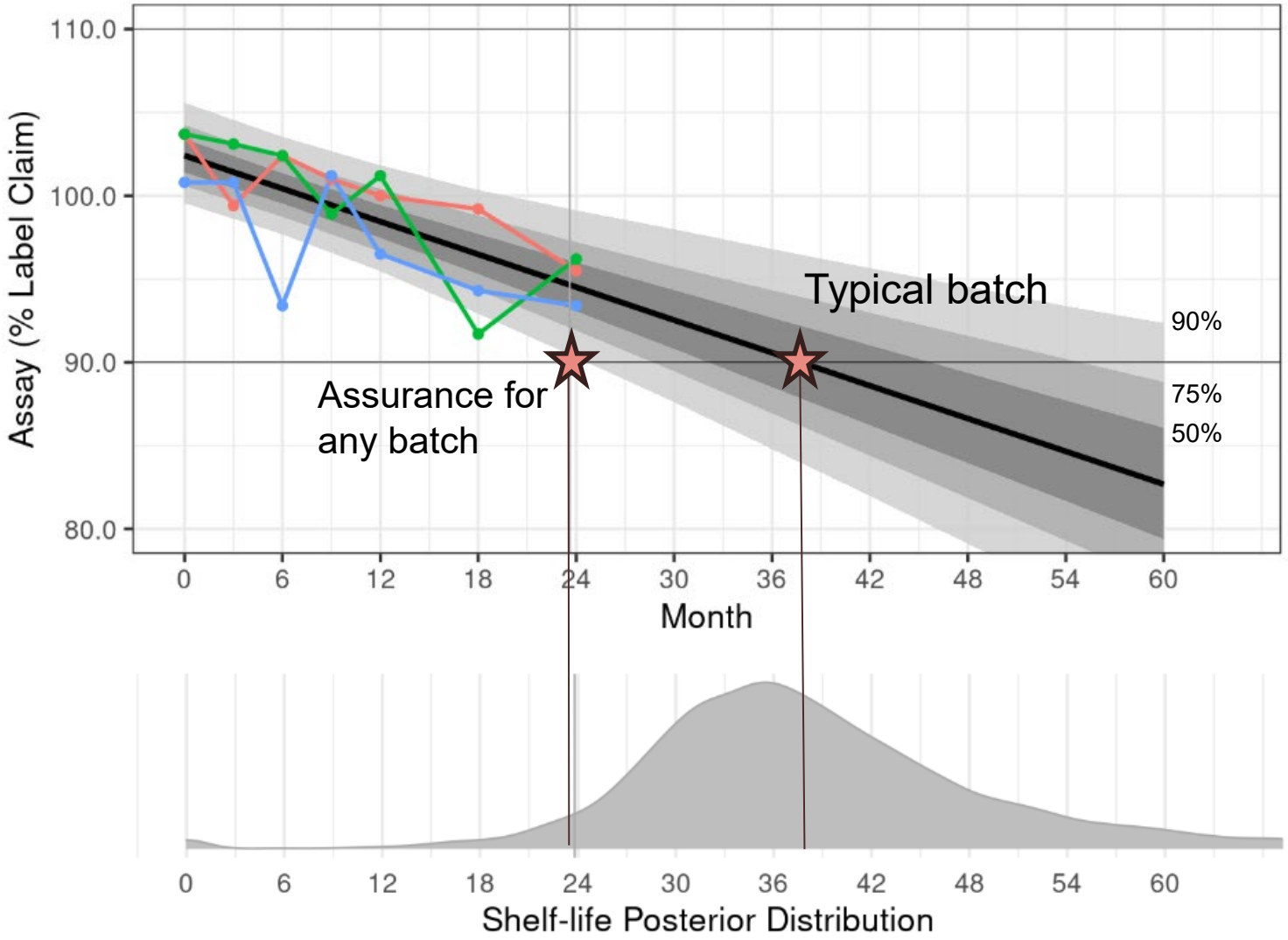
Bayesian stability model

- Weakly informative priors utilized for most model parameters (e.g. batch release, change on stability)
  - The *a priori* assumption is a very limited shelf-life
- Incorporate prior knowledge for between-batch variability for release and stability change

Altan, S., Faya, P., Rauk, A. P., LeBlond, D., Seaman Jr, J. W., & Banton, D. (2023). Stability analysis using mixed models: A critique of tolerance interval methods and a probabilistic solution. *Pharmaceutical Statistics*.



Bayesian stability model



- Model provides predicted Assay (% Label Claim) at a given time
- Directly translates to shelf-life distribution
- At 23.6 months there is 95% probability that any given batch remains within specification acceptance criteria

Inference Statements

Bayesian Model

- For any given future batch from the process, there is a 95% probability that it will remain within specifications for the shelf-life duration (23.6 months)
- Inference applies to future batches

ICH Q1E

- For the three batches in the analysis, there is 95% confidence that all will remain within specifications for the shelf-life duration (25.1 months)
- Inference is specific to the batches in the study

Prior Knowledge

Bayesian Model

- Likely magnitude of batch variability defined via probability distribution

ICH Q1E

- Assumes no variation in change on stability between batches

Sources of prior information

Molecule Specific

Method variability

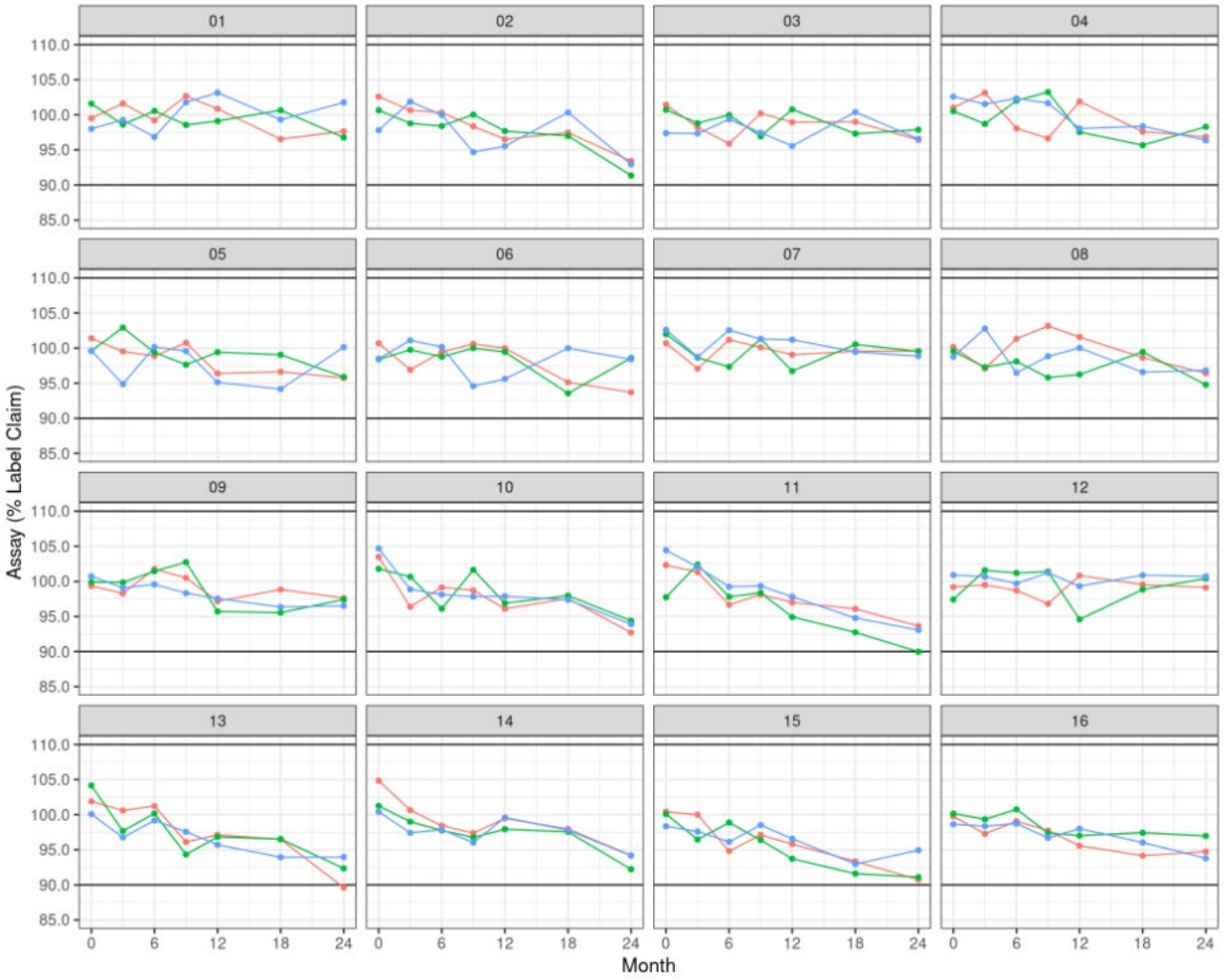
Batch release variability

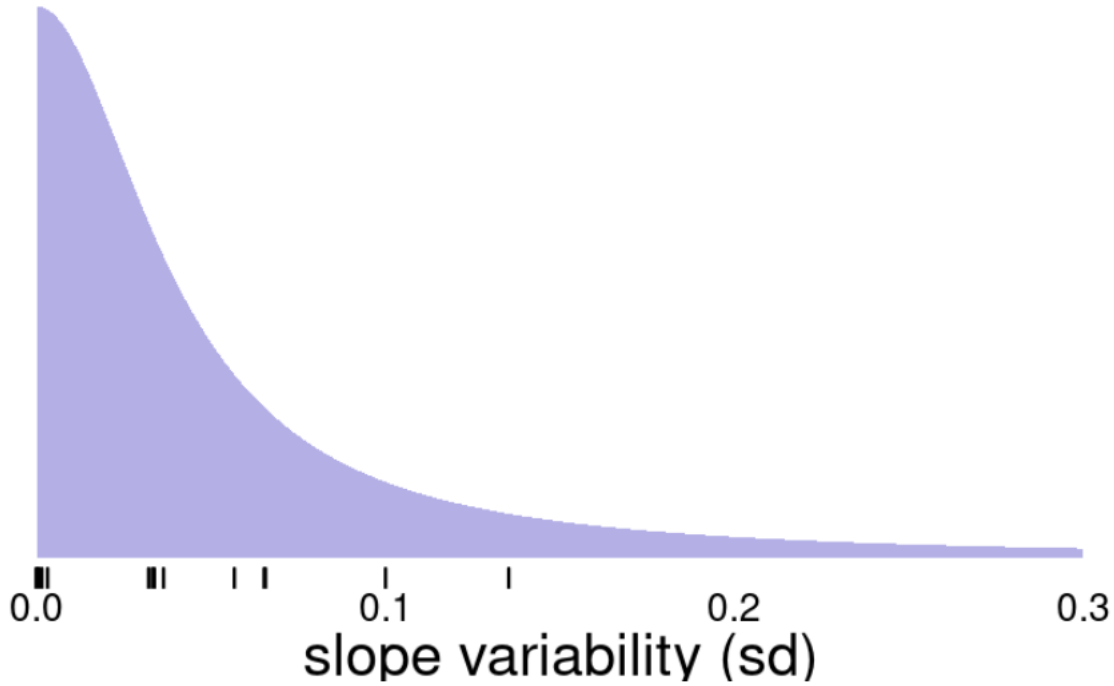
Accelerated stability

Platform Knowledge

Quantifies variation in parameters between molecules

Platform knowledge (hypothetical 16-molecule example)





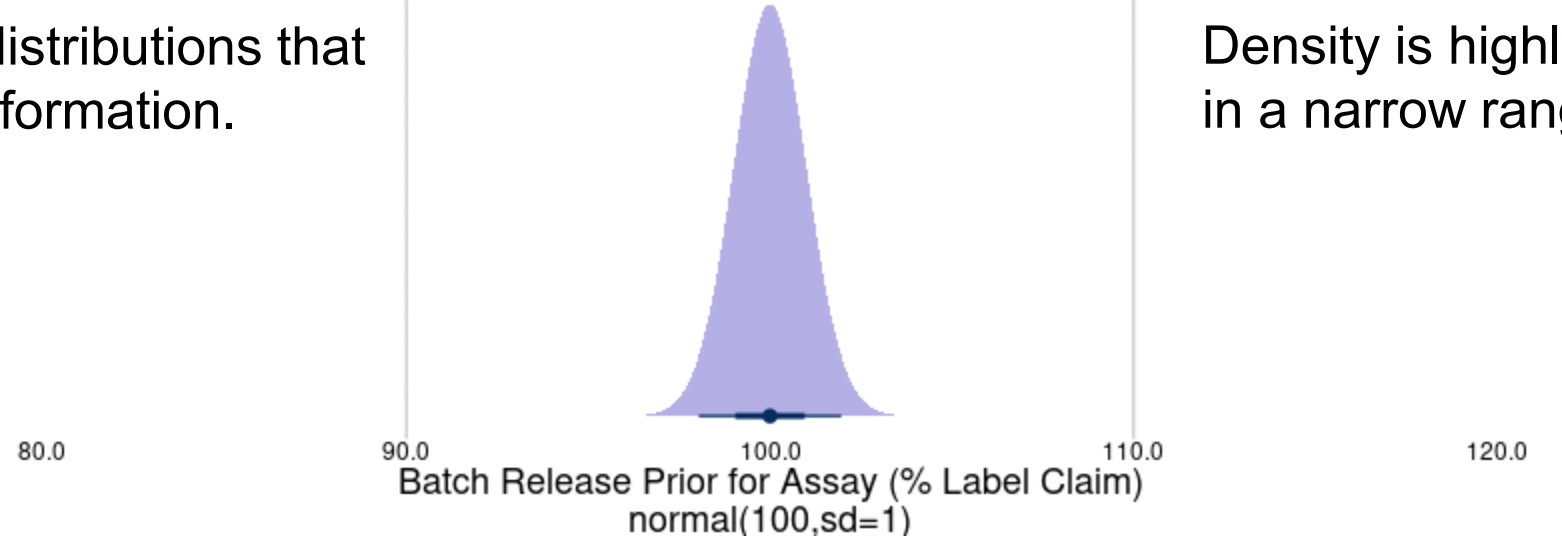
Measurements for each molecule shown in number line

Prior Distributions

Non-informative → **Informative**

Very diffuse distributions that impart little information.

Density is highly concentrated in a narrow range.



- There are varying degrees of informativeness
- Opportunity for discussion
  - sponsor proposes the prior
  - may be modified based on feedback

Conclusions

- Bayesian methodology offers a tool to directly combine empirical data with prior knowledge
- Enables probabilistic inference that applies to future batches

- Provides a useful way to leverage prior knowledge and improve decision making for the molecule

Thank you