BAYESIAN BIOSTATISTICS CONFERENCE 2025
LEIDEN, THE NETHERLANDS

Bayesian Decision Limits for Correlated Analytes: A Multivariate Regression Approach with Non-Informative and Conjugate Priors

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Research Background & Motivation

Clinical
Decision Limits

play an important role in laboratory medicine as they guide healthcare professionals in their diagnostic and decision-making processes.

REFERENCE RANGES vs DECISION LIMITS

Reference Ranges

→ Values typical in a healthy population
→ Help identify unusual results (not necessarily disease)
→ E.g. Fasting glucose: **70–100 mg/dL**

Decision Limits

→ Clinically defined thresholds for diagnosis or intervention.
→ Cross threshold = likely illness
→ E.g. **≥126 mg/dL → Diabetes**

In practice, **univariate statistical intervals** are commonly used as decision limits.

Why Go Beyond Univariate Limits?

In real clinical scenarios, multiple biomarkers are often used together to make a diagnosis. Some examples are:

- Drug Induced Liver Injury (Hepatotoxicity) – ALT, AST, bilirubin, etc.
- Assessment of Kidney Function – urea, uric acid creatinine

Problem: Separate univariate limits = increase in the false-positive rate

Solution: Multivariate decision regions that account for the correlation among analytes.

Ellipsoidal Regions

- Unable to detect component-wise outliers
- Not suitable for the computation of one-sided limits

→

Rectangular Regions

In the frequentist approach, recent studies proposed to construct rectangular tolerance and prediction regions using parametric bootstrap

Why Bayesian?

- **Frequentist methods** for multivariate tolerance intervals are often **only approximate**, since it is much harder to obtain an exact solution that accounts for the correlations among analytes.
- **Bayesian approaches**, like those proposed by Liu et al. (2022):
  - Offer a more flexible and interpretable framework.
  - Allow prior knowledge and uncertainty to be incorporated.

What if we add covariates?

- Allows decision thresholds to adjust based on patient covariates (e.g., age, weight, height).
- Personalized diagnostics

Our Contribution

- This study proposes a **Bayesian framework for regression-based decision limits**
- This approach also
  - Accounts for multiple analytes and their correlations
  - Integrates the tolerance criterion

Covariates

\+

Decision Limits

\+

Multiple Analytes

\+

Tolerance

\+

Bayesian Framework

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Methodology

Preliminaries

Suppose we have multivariate linear regression model given by

$$\mathbf{Y} = \mathbf{B}\mathbf{X} + \mathbf{E} \qquad \text{where } \mathrm{vec}\,(\mathbf{E}) \sim N_{np}(\mathbf{0}, \boldsymbol{I}_n \otimes \boldsymbol{\Sigma}).$$

Based on the given regression model, the likelihood function is given by

$$L(\mathbf{B}, \boldsymbol{\Sigma} | \mathbf{Y}) \quad \propto |\boldsymbol{\Sigma}|^{-n/2} \exp\left\{-\frac{1}{2}\ \mathrm{tr}\ [\boldsymbol{\Sigma}^{-1}(\mathbf{Y} - \mathbf{B}\mathbf{X})(\mathbf{Y} - \mathbf{B}\mathbf{X})']\right\}$$

Note that the least squares estimators of $\mathbf{B}$ and $\boldsymbol{\Sigma}$ are:

$$\widehat{\mathbf{B}} = \mathbf{Y}\mathbf{X}'(\mathbf{X}\mathbf{X}')^{-1} \qquad \mathbf{S} = \frac{1}{n-q}\left(\mathbf{Y} - \widehat{\mathbf{B}}\mathbf{X}\right)\left(\mathbf{Y} - \widehat{\mathbf{B}}\mathbf{X}\right)'$$

Non-Informative

Prior distribution:

$$p(\mathbf{B}, \boldsymbol{\Sigma}) \propto |\boldsymbol{\Sigma}|^{-\frac{1}{2}(p+1)}$$

Posterior distribution:

$$\text{vec}\,(\mathbf{B})|\boldsymbol{\Sigma}, \mathbf{Y} \sim N_{pq}\left(\text{vec}\,(\widehat{\mathbf{B}}), (\mathbf{XX}')^{-1} \otimes \boldsymbol{\Sigma}\right)$$

$$\boldsymbol{\Sigma}|\mathbf{Y} \sim \text{Inv}-\text{Wishart}((n-q)\mathbf{S}, n-q)$$

Conjugate

Prior distribution:

$$\text{vec}\,(\mathbf{B})|\boldsymbol{\Sigma} \sim N_{pq}(\text{vec}\,(\mathbf{B}_0), \mathbf{V}_0 \otimes \boldsymbol{\Sigma})$$

$$\boldsymbol{\Sigma} \sim \text{Inv}-\text{Wishart}\left(\mathbf{Q}_0, \nu_0\right)$$

Posterior distribution:

$$\text{vec}\,(\mathbf{B})|\boldsymbol{\Sigma}, \mathbf{Y} \sim N_{pq}(\text{vec}\,(\mathbf{B}_n), \mathbf{V}_n \otimes \boldsymbol{\Sigma})$$

$$\boldsymbol{\Sigma}|\mathbf{Y} \sim \text{Inv}-\text{Wishart}(\mathbf{Q}_n, \nu_n)$$

$$\mathbf{B}_n = \left(\mathbf{B}_0\mathbf{V}_0^{-1} + \widehat{\mathbf{B}}\mathbf{XX}'\right)(\mathbf{V}_0^{-1} + \mathbf{XX}')^{-1}$$

$$\mathbf{V}_n = (\mathbf{V}_0^{-1} + \mathbf{XX}')^{-1}$$

$$\mathbf{Q}_n = \mathbf{Q}_0 + (\mathbf{Y} - \mathbf{XB}_n)(\mathbf{Y} - \mathbf{XB}_n)' + (\mathbf{B}_n - \mathbf{B}_0)\mathbf{V}_0^{-1}(\mathbf{B}_n - \mathbf{B}_0)'$$

$$\nu_n = n + \nu_0$$

Construction of Decision Limits

Let $\boldsymbol{Y}_0$ be a $p \times 1$ vector representing **a future sample observation** corresponding to the $q \times 1$ vector of covariates $\boldsymbol{x}_0$, where the two are related as

$$\boldsymbol{Y}_0 | \mathbf{B}, \boldsymbol{\Sigma} \sim N_p(\mathbf{B}\boldsymbol{x}_0, \boldsymbol{\Sigma})$$

Write $\boldsymbol{Y}_0 = (y_1, y_2, \ldots, y_p)'$. We define the region S as

$$\mathbf{S}(\boldsymbol{x}_0) = \left\{ \boldsymbol{Y}_0 \middle| \boldsymbol{y}_1 > \boldsymbol{a}_1(\boldsymbol{x}_0), \boldsymbol{y}_2 > \boldsymbol{a}_2(\boldsymbol{x}_0), \ldots, \boldsymbol{y}_p > \boldsymbol{a}_p(\boldsymbol{x}_0) \right\}$$

Note: Using this region, a person is declared "positive" if and only if $\boldsymbol{Y}_0 \in S(\boldsymbol{x}_0)$, i.e., **all the measurements exceed their corresponding decision limits**.

Decision limits:

$$\mathbf{a_i} = \left(\widehat{\mathbf{B}}\mathbf{x_0}\right)_{\mathbf{i}} + \boldsymbol{\kappa}\sqrt{\mathbf{S_{ii}}}$$

Bayesian Tolerance Intervals

To control the false positive rate (FPR) 1-β with a certain confidence level 1-α, we specify the **β-content, $(1-\alpha)$-confidence Bayesian tolerance region:**

$$P_{\mathbf{B},\boldsymbol{\Sigma}|\mathbf{Y}}\left\{P_{\boldsymbol{Y}_0|\mathbf{B},\boldsymbol{\Sigma}}\left\{\boldsymbol{Y}_0 \in \bar{S}(\boldsymbol{x}_0;\kappa_s)\right\} \geq \beta\right\} = 1-\alpha$$

where β is a number close to 1 and $\bar{S}(\mathbf{x}_0;\kappa_s)$ is the complement of S .

Why Tolerance Intervals?

→ Aim to cover a specified proportion of the population with confidence.

→ Allow **repeated use** in diagnosing multiple patients.

Algorithm 1. *Computation of regression-based statistical decision limits using Bayesian tolerance regions*

For a given set of observations $\boldsymbol{Y}_\alpha, \boldsymbol{x}_\alpha, \alpha = 1, 2, \ldots, n$ and $\boldsymbol{x}_0$.

Repeat L times (steps 2–3)

1. Compute $\widehat{\mathbf{B}}$ and $\mathbf{S}$.

2. Generate one value of $\boldsymbol{\Sigma}^{(l)}$ and $\mathbf{B}^{(l)}$:

   $\boldsymbol{\Sigma}^{(l)} \sim$ Inv−Wishart

   $\text{vec}\left(\mathbf{B}^{(l)}\right) | \boldsymbol{\Sigma}^{(l)} \sim$ Multivariate Normal

3. Solve for the tolerance factor κ such that

   $P_{\boldsymbol{Y}_0 | \mathbf{B}^{(l)}, \boldsymbol{\Sigma}^{(l)}}\{\boldsymbol{Y}_0 \in S(\boldsymbol{x}_0; \kappa)\} = 1 - \beta.$

4. $\kappa_1, \kappa_2, \ldots, \kappa_L$

Take the $(1-\alpha)$-quantile

5. $\tilde{\kappa}$

6. Decision Limits

   $a_i = \left(\widehat{\mathbf{B}}\boldsymbol{x}_0\right)_i + \tilde{\kappa}\sqrt{\mathbf{S}_{ii}}$

Application

Predicting Hospital Mortality using SOFA and APACHE II scores

We use the data in the study by Jung et al. (2018) which discusses the effect of increased phosphate levels in the severity of acute kidney injury (AKI) among patients undergoing continuous renal replacement therapy (CRRT).

Response vector: $\boldsymbol{Y} = [\text{SOFA score},\ \text{APACHE II score}]'$

Covariate vector: $\boldsymbol{x} = [1, \text{age, sex, CCI, MAP, UO, Phosphate}]'$

Decision regions were constructed for both male and female patients with **CCI = 3.2**, **MAP = 77.8 mmHg**, and **UO = 71.4 mL.**

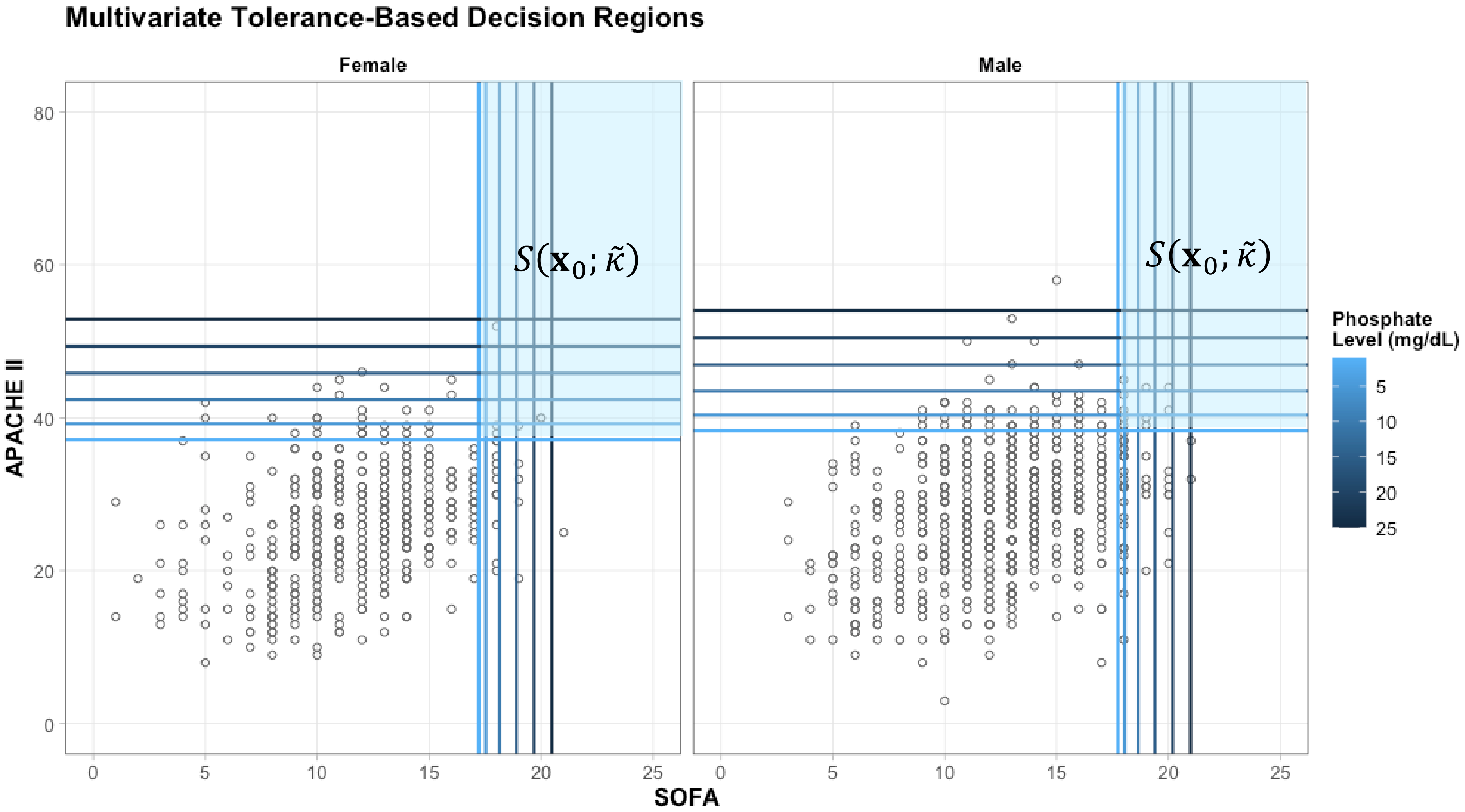

Figure 4.3.1. Bayesian multivariate decision regions for SOFA and APACHE II scores using a one-sided 0.99-content, 0.95-confidence tolerance criterion under a non-informative prior. The decision regions are for female and male patients by phosphate level, with age = 63, CCI = 3.2, MAP = 77.8 mmHg, UO = 71.4 mL.

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Simulation Studies

Assessing the performance

Although the proposed decision limits have been derived through a Bayesian criterion, it may also be of interest to study its **frequentist properties**.

We want to see if the following condition holds:

$$P_{\widehat{\mathbf{B}},\widehat{\mathbf{\Sigma}}}\{P_{\mathbf{Y}_0}\{\mathbf{Y}_0 \in \overline{S}(\mathbf{x}_0;\kappa)\big|\widehat{\mathbf{B}},\widehat{\mathbf{\Sigma}}\} \geq \beta\} = 1-\alpha$$

That is, we shall be computing for their **coverage probabilities**.

1. Generate $\boldsymbol{Y}_\alpha \sim N_p(\mathbf{B}\boldsymbol{x}_\alpha, \mathbf{\Sigma})$, $\alpha = 1, 2, \ldots, n$
2. Compute decision limits to obtain the decision region $S(\mathbf{x}_0;\tilde{\kappa})$
3. $P_{\boldsymbol{Y}_0}\left(\boldsymbol{Y}_0 \in \overline{S}(\mathbf{x}_0;\tilde{\kappa})\right) = 1 - P_{\boldsymbol{Y}_0}(\boldsymbol{Y}_0 \in S(\mathbf{x}_0;\tilde{\kappa}))$

Repeat M times

4. Compute proportion of times $P_{\boldsymbol{Y}_0}\left(\boldsymbol{Y}_0 \in \overline{S}(\mathbf{x}_0;\tilde{\kappa})\right) \geq \beta$

Simulation Setup

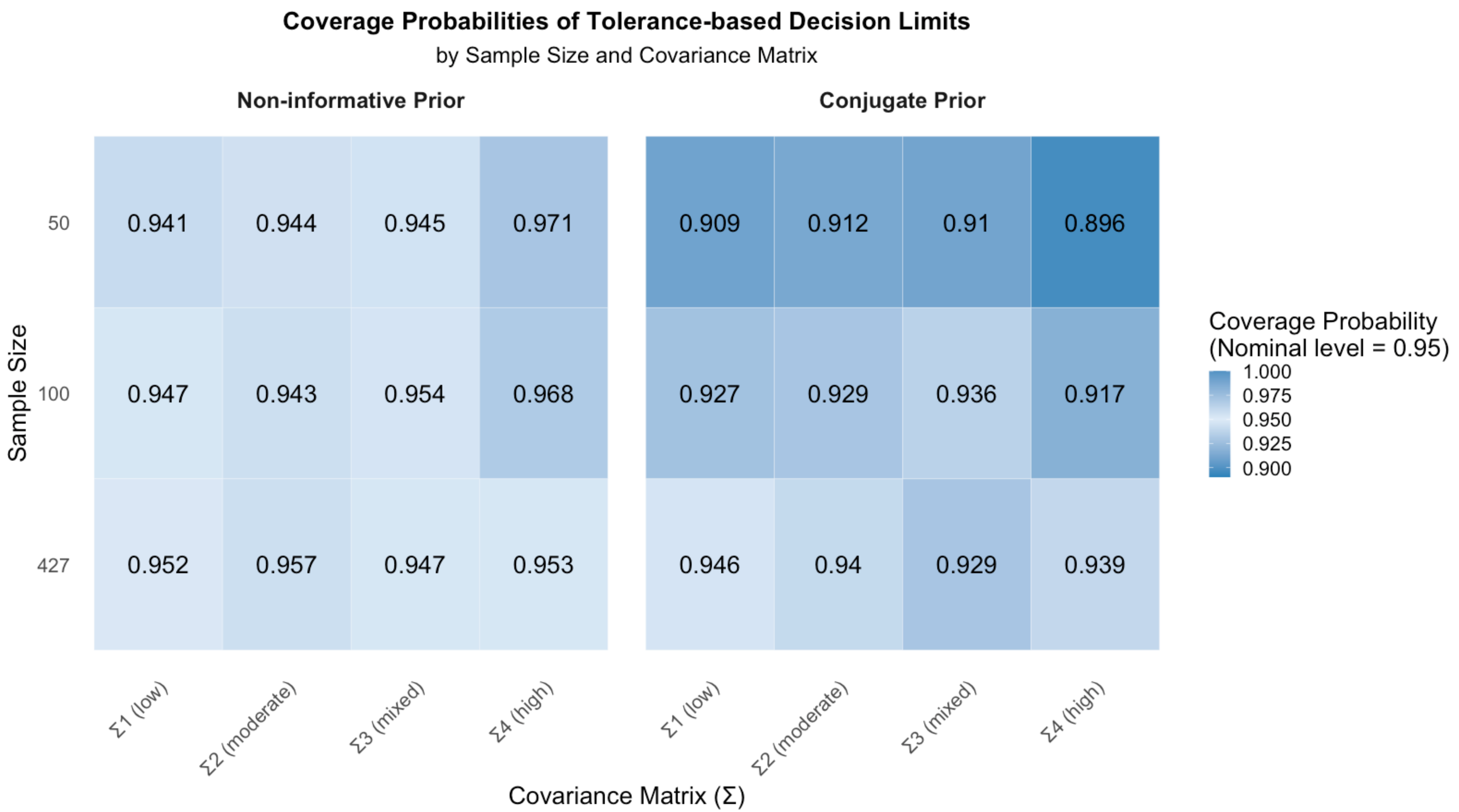
- Data taken from **Mattsson et al. (2008).**
- **Response vector:**

$$\boldsymbol{Y} = [\ln(\text{S-IGF-I}), (\text{S-IGFBP-2})^{0.25}, \ln(\text{S-IGFBP-3})]'$$

- **Covariates** (sex: 0 – males, 1 – females)**:**

$$\boldsymbol{x} = [1, \text{age} - 45, (\text{age} - 45)^2, \text{sex}, \text{BMI} - 25]'$$

- Simulations conducted using **4 covariance structures** (low, moderate, mixed, high)
- **Sample sizes**: $n = 50, 100, \text{and } 427$
- **Posterior Draws**: L = 1000
- **Parameters:** $\beta = 0.999$ and $1 - \alpha = 0.95$
- **Simulation Samples:** M = 5000


Coverage Probabilities of Tolerance-based Decision Limits
by Sample Size and Covariance Matrix
Non-informative Prior
Conjugate Prior
Sample Size
50
100
427
0.941
0.944
0.945
0.971
0.947
0.943
0.954
0.968
0.952
0.957
0.947
0.953
0.909
0.912
0.91
0.896
0.927
0.929
0.936
0.917
0.946
0.94
0.929
0.939
Σ1 (low)
Σ2 (moderate)
Σ3 (mixed)
Σ4 (high)
Covariance Matrix (Σ)
Coverage Probability
(Nominal level = 0.95)
1.000
0.975
0.950
0.925
0.900

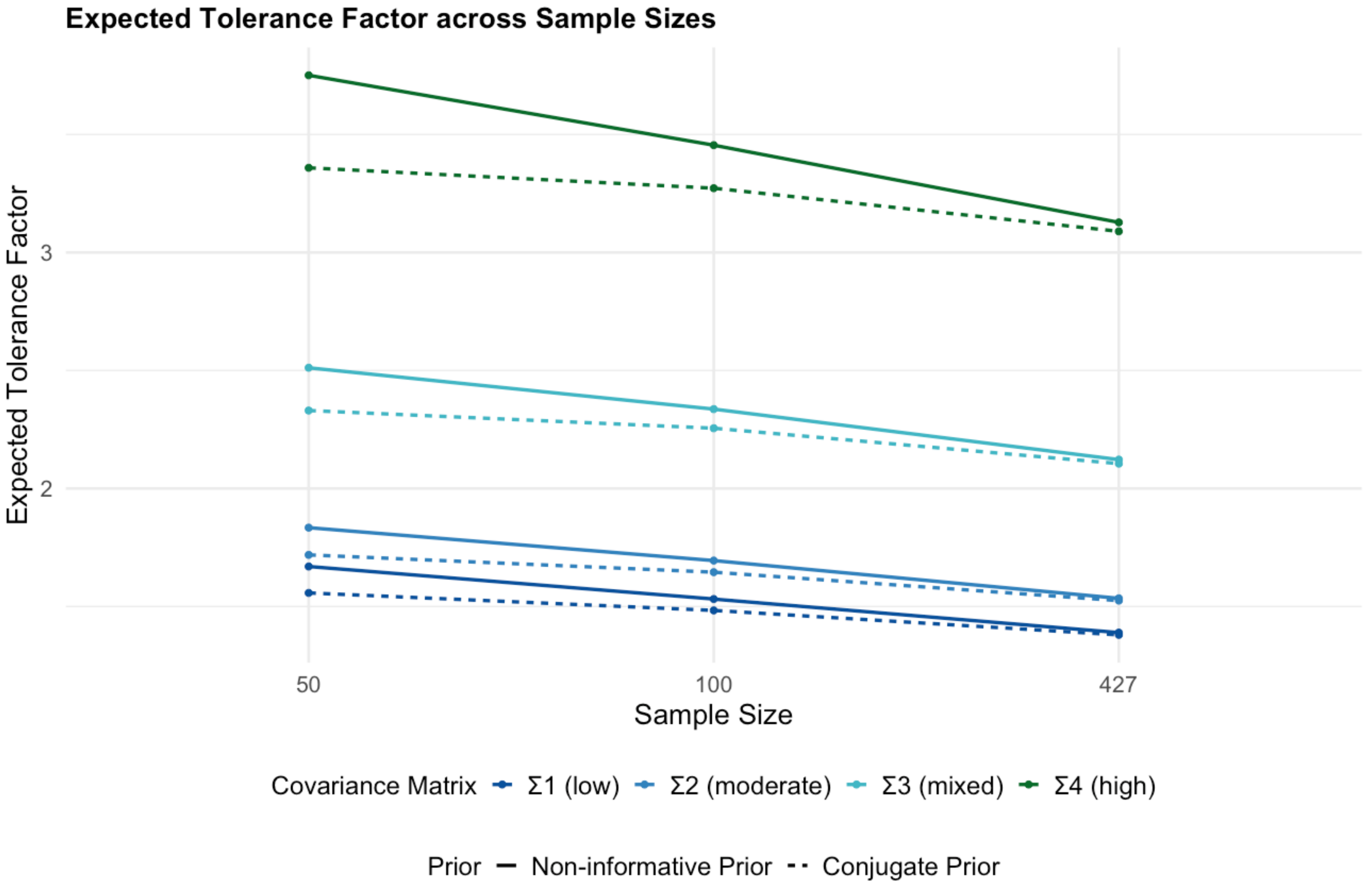
SIMULATION RESULTS

- Due to the influence of the prior, these decision limits computed under a conjugate prior may not yield coverage probabilities close to the nominal level when evaluated using a frequentist approach.

- However, this prior influence will be dominated by the data as the sample size increases, resulting to coverage probabilities closer to 0.95.

Estimated Tolerance Factor

The expected value of the tolerance factor $E(\tilde{\kappa})$, **decreases as sample size increases**, reflecting the reduced uncertainty in larger samples.



SIMULATION RESULTS

For L=1000, it takes more or less three seconds, on the average, to compute for the tolerance-based decision limits.

Sample Size	Covariance	Non-informative	Conjugate
n = 50	Σ_1	2.71	3.39
	Σ_2	3.05	3.20
	Σ_3	2.90	3.29
	Σ_4	3.59	3.06
n = 100	Σ_1	2.75	3.27
	Σ_2	2.64	3.23
	Σ_3	5.96	3.49
	Σ_4	3.62	3.23
n = 427	Σ_1	2.60	3.32
	Σ_2	2.72	3.24
	Σ_3	6.07	3.52
	Σ_4	3.40	3.26

CONCLUSION

- The tolerance-based decision limits constructed under the **non-informative prior** have highly satisfactory frequentist properties, with coverage probabilities close to the nominal levels.
- The decision limits computed under a conjugate prior have coverage probabilities less than the set nominal level, which may be due to the influence of the prior distribution of the parameters
- Furthermore, the proposed methodology is also efficient and fast enough for practical purposes as it takes **more or less three seconds** to compute decision limits for about L=1,000 Monte Carlo samples on the average.

Some Recommendations

To further enhance the methodologies proposed, several things may also be worth investigating in the future.

Optimize prior distribution and hyperparameter selection

Explore the coverage probabilities at larger Monte Carlo samples

Consider other forms of the decision regions

Explore constructing decision regions under a distribution-free setting

Bayesian Prediction Intervals

We require that:

$$P_{\boldsymbol{Y}_0|\mathbf{Y}}\{\boldsymbol{Y}_0 \in S(\boldsymbol{x}_0;\kappa)\} = 1-\beta$$

$$\Leftrightarrow \; P_{\boldsymbol{Y}_0|\mathbf{Y}}\left(y_1 > \left(\widehat{\mathbf{B}}\boldsymbol{x}_0\right)_1 + \kappa\sqrt{\mathbf{S}_{11}}, \ldots, y_p > \left(\widehat{\mathbf{B}}\boldsymbol{x}_0\right)_p + \kappa\sqrt{\mathbf{S}_{pp}}\right) = 1-\beta$$

$$\Leftrightarrow \; P_{\boldsymbol{Y}_0|\mathbf{Y}}\left(\min_{1\le i\le p}\left\{\frac{y_i - \left(\widehat{\mathbf{B}}\boldsymbol{x}_0\right)_i}{\sqrt{\mathbf{S}_{ii}}}\right\} > \kappa\right) = 1-\beta$$

Algorithm 2. *Computation of regression-based statistical decision limits using Bayesian prediction regions*

For a given set of observations $\boldsymbol{Y}_\alpha, \boldsymbol{x}_\alpha, \alpha = 1, 2, \ldots, n$ and $\boldsymbol{x}_0$.

1. Compute $\hat{\mathbf{B}}$ and $\mathbf{S}$.

Repeat L times

2. Generate $\boldsymbol{\Sigma}^{(l)}$ and $\mathbf{B}^{(l)}$:
   $\boldsymbol{\Sigma}^{(l)} \sim$ Inv−Wishart
   vec $\left(\mathbf{B}^{(l)}\right) | \boldsymbol{\Sigma}^{(l)} \sim$ Multivar Normal

3. Given the values, generate
   $\boldsymbol{Y}_0^{(l)} \sim N_p\left(\mathbf{B}^{(l)}\boldsymbol{x}_0, \boldsymbol{\Sigma}^{(l)}\right)$

4. Compute:
   $$\kappa_{NI,l} = \min_{1 \le i \le p} \left\{ \frac{y_i^{(l)} - \left(\hat{\mathbf{B}}\boldsymbol{x}_0\right)_i}{\sqrt{\mathbf{S}_{ii}}} \right\}$$

5. $\kappa_1, \kappa_2, \ldots, \kappa_L$

Take the β-quantile

6. $\tilde{\kappa}$

7. Decision Limits
   $a_i = \left(\hat{\mathbf{B}}\boldsymbol{x}_0\right)_i + \tilde{\kappa}\sqrt{\mathbf{S}_{ii}}$

Coverage Probabilities – Prediction Criterion

Sample size	Covariance matrix	Non-informative	Conjugate
$n = 50$	$\boldsymbol{\Sigma}_1$ (low)	0.993	0.987
	$\boldsymbol{\Sigma}_2$ (moderate)	0.988	0.988
	$\boldsymbol{\Sigma}_3$ (mixed)	0.990	0.990
	$\boldsymbol{\Sigma}_4$ (high)	0.990	0.985
$n = 100$	$\boldsymbol{\Sigma}_1$ (low)	0.989	0.991
	$\boldsymbol{\Sigma}_2$ (moderate)	0.990	0.991
	$\boldsymbol{\Sigma}_3$ (mixed)	0.991	0.989
	$\boldsymbol{\Sigma}_4$ (high)	0.991	0.987
$n = 427$	$\boldsymbol{\Sigma}_1$ (low)	0.990	0.990
	$\boldsymbol{\Sigma}_2$ (moderate)	0.990	0.990
	$\boldsymbol{\Sigma}_3$ (mixed)	0.990	0.989
	$\boldsymbol{\Sigma}_4$ (high)	0.990	0.988

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FIN

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