**An R Package for Simulating Multivariate Environmental Exposure Data and Estimating Feature Selection Thresholds for Bayesian Kernel Machine Regression**

**Abstract**

**We present an R package designed to assist researchers and analysts in simulating multivariate environmental exposure data and estimating feature selection thresholds for Bayesian Kernel Machine Regression (BKMR). This package provides tools to generate multivariate data from distributions commonly found in environmental health studies, including multivariate normal and skewed Gamma distributions. Additionally, it offers functionality to calculate important statistical features such as mean, variance, skewness, and correlation, as well as the Posterior Inclusion Probability (PIP) threshold, which is crucial for feature selection in BKMR. This package is particularly useful in settings where environmental exposure data deviate from normality, making it a valuable tool for researchers working with complex datasets.**

**Keywords**

**R package, Bayesian Kernel Machine Regression, multivariate simulation, feature selection, environmental exposure, statistical moments, Gamma distribution, skewed Gamma distribution, non-normal data**

**1. Introduction**

**Environmental exposure to pollutants such as Cadmium, Mercury, Arsenic, and Lead is a significant risk factor for a variety of health issues, particularly in vulnerable populations such as children. These exposures are typically measured in multivariate datasets, where the data may exhibit skewness, non-normal distributions, and correlations between multiple environmental factors. Accurate modeling and analysis of these datasets require sophisticated statistical methods.**

**Bayesian Kernel Machine Regression (BKMR) is a widely used approach for identifying important environmental factors and interactions, but it often assumes normality in the data. In real-world datasets, particularly in environmental health studies, data frequently deviate from normality, with many variables following skewed distributions. This limitation in BKMR can affect its performance and feature selection accuracy.**

**This R package addresses this gap by providing tools for simulating multivariate environmental exposure data from distributions commonly found in environmental health studies, including multivariate normal and skewed Gamma distributions. The package also includes functionality to calculate the Posterior Inclusion Probability (PIP) threshold, which is essential for feature selection in BKMR when working with non-normal data.**

**2. Materials and Methods**

**2.1. Overview of the R Package**

**The primary goal of this R package is to provide tools for simulating multivariate environmental exposure data and estimating feature selection thresholds for Bayesian Kernel Machine Regression (BKMR). The package includes the following core functions:**

* **Data Simulation Functions: These functions generate multivariate data from distributions commonly used in environmental health studies. Key functions include:**
  + **simulate\_group\_data: Simulates data for multiple groups using multivariate normal or Gamma distributions.**
  + **simulate\_group\_gamma: Specifically generates multivariate Gamma data, including skewed Gamma distributions.**
  + **simulate\_group\_gaussian: Generates multivariate normal data for groups with normal distribution assumptions.**
  + **generate\_mvGamma\_data: Generates multivariate skewed Gamma data, transforming multivariate normal data to match skewed distributions commonly seen in environmental health data.**
* **Statistical Moment Estimation: The estimate\_mv\_moments function computes essential statistical features, such as mean, variance, skewness, and correlation matrix. These moments help characterize the underlying data and are necessary for feature selection in BKMR.**
* **Feature Selection Threshold Calculation: The calculate\_pip\_threshold function estimates the Posterior Inclusion Probability (PIP) threshold for feature selection in BKMR, using Richard’s Four-Parameter Logistic Regression (Richard’s curve). The PIP threshold is vital for identifying important features while maintaining nominal test size.**

**2.2. Data Simulation Methods**

**The package offers several functions for simulating multivariate data from distributions commonly found in environmental health studies:**

* **Multivariate Normal Distribution: The function simulate\_group\_gaussian generates data based on the multivariate normal distribution. This is useful when the data are approximately normally distributed.**
* **Multivariate Gamma Distribution: The simulate\_group\_gamma function generates multivariate Gamma-distributed data, which is useful for modeling environmental exposure data that are positively skewed and exhibit heavy tails, such as Cadmium and Mercury levels.**
* **Multivariate Skewed Gamma Distribution: The function generate\_mvGamma\_data generates skewed Gamma-distributed data by first generating multivariate normal samples, transforming them into Z-scores, and then applying the Gamma transformation using the qgamma function. This is particularly useful for modeling data that exhibits strong skewness, as is often the case in environmental exposure datasets.**

**2.3. Statistical Moment Estimation**

**To help researchers understand the structure of the simulated data, the estimate\_mv\_moments function calculates the following statistical features:**

* **Sample Size: The number of observations in each group.**
* **Mean Vector: The mean of each variable in the multivariate data.**
* **Standard Deviation Vector: The standard deviation for each variable.**
* **Skewness: The skewness of each variable, which indicates the asymmetry of the data.**
* **Correlation Matrix: The correlation structure between the variables.**

**These statistical moments are essential for understanding the underlying data distribution and are useful for the feature selection process in BKMR.**

**2.4. Feature Selection and Threshold Estimation**

**The key functionality for feature selection in BKMR is the PIP threshold calculation, which is done using the calculate\_pip\_threshold function. This function estimates the PIP threshold using a Richard’s Four-Parameter Logistic Regression model. The PIP threshold ensures that BKMR retains a nominal 5% test size, even in the presence of skewed or non-normally distributed data.**

**The Richard’s Four-Parameter Logistic Regression model is represented by the formula:**

**PIP(q95)=A+K−A(C+exp⁡(−β1⋅x1))β2⋅x2PIP(q\_{95}) = A + \frac{K - A}{ (C + \exp(-\beta\_1 \cdot x\_1) )^{\beta\_2 \cdot x\_2} }PIP(q95​)=A+(C+exp(−β1​⋅x1​))β2​⋅x2​K−A​**

**Where:**

* **AAA: Left asymptote (fixed at 0).**
* **KKK: Right asymptote.**
* **CCC: Constant.**
* **β1,β2\beta\_1, \beta\_2β1​,β2​: Midpoint shift parameters for CV and sample size.**
* **x1x\_1x1​: Log-transformed CV.**
* **x2x\_2x2​: Log-transformed sample size.**

**2.5. Data Transformation Functions**

**The package also includes a set of data transformation functions to help ensure that the data is appropriately scaled and normalized for analysis:**

* **Scaling by Standard Deviation or MAD: The trans\_ratio function scales data by either the standard deviation (SD) or the median absolute deviation (MAD), ensuring proper normalization.**
* **Logarithmic and Root Transformations: The trans\_log function applies a logarithmic transformation, and the trans\_root function applies fractional root transformations. These transformations help handle skewed data and improve model fitting.**

**3. Software Implementation**

**3.1. Installation**

**The R package is available on CRAN and can be installed using the following command:**

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**install.packages("name\_of\_your\_package")**

**Alternatively, if the package is hosted on GitHub, it can be installed using the devtools package:**

**r**

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**devtools::install\_github("username/name\_of\_your\_package")**

**3.2. Package Functions**

**The package provides several key functions to simulate and analyze environmental exposure data:**

* **simulate\_group\_gaussian: Generates multivariate normal data.**

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**simulate\_group\_gaussian(param\_list, group\_col\_name)**

* **simulate\_group\_gamma: Generates multivariate Gamma data.**

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**simulate\_group\_gamma(param\_list, group\_col\_name)**

* **generate\_mvGamma\_data: Generates skewed Gamma data from multivariate normal data.**

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**generate\_mvGamma\_data(sampSize, mean\_vec, sampCorr\_mat, shape\_num, rate\_num)**

* **estimate\_mv\_moments: Estimates statistical moments for a group of data.**

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**estimate\_mv\_moments(x\_df)**

* **calculate\_pip\_threshold: Estimates the PIP threshold for feature selection in BKMR.**

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**calculate\_pip\_threshold(y, absCV, sampSize, coeffs\_ls)**

**3.3. Example Usage**

**To simulate data and calculate PIP thresholds, follow these examples:**

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**# Example for simulating multivariate normal data**

**param\_list <- list(**

**Group1 = list(mean\_vec = c(1, 2), sampCorr\_mat = matrix(c(1, 0.5, 0.5, 1), 2, 2), sampSize = 100),**

**Group2 = list(mean\_vec = c(2, 3), sampCorr\_mat = matrix(c(1, 0.3, 0.3, 1), 2, 2), sampSize = 150)**

**)**

**simulated\_data <- simulate\_group\_gaussian(param\_list, "Group")**

**# Example for calculating PIP threshold**

**pip\_threshold <- calculate\_pip\_threshold(y = response\_data, absCV = 0.05, sampSize = 100)**

**4. Real-World Scenario**

**1. Dataset Overview**

**The data used in this study is sourced from the *Taranto Children Study*, which includes information on children's IQ scores, metal concentrations (Cadmium, Mercury, Arsenic, Lead, and Manganese), and gender. The dataset was pre-processed to remove missing values, and only the relevant variables—IQ, metal concentrations, and gender—were retained for analysis.**

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**library(bkmr)**

**library(simBKMRdata)**

**library(tidyverse)**

**# Load the dataset**

**bkmrAnalysisData\_df <- data("metalExposChildren\_df")**

**# Preprocess the data by selecting relevant columns and removing missing values**

**bkmrAnalysisData\_df <- metalExposChildren\_df %>%**

**select(QI, Cadmium:Manganese, Sex) %>%**

**na.omit() %>%**

**mutate(**

**across(Cadmium:Manganese, ~ trans\_log(.))**

**)**

**2. Estimation of Moments for Multivariate Skewed Gamma Distribution**

**To appropriately model the skewed nature of the metal exposure data, we estimate the moments (mean, variance, and skewness) of each metal using a multivariate skewed gamma distribution. This distribution was chosen because metal concentrations often exhibit right skewness and heteroscedasticity, making it a suitable model for these variables.**

**4. Bayesian Kernel Machine Regression (BKMR)**

**Bayesian Kernel Machine Regression (BKMR) was employed to investigate the effects of metal exposures on children's IQ scores. This method allows for non-linear relationships between predictors (metal exposures) and the outcome (IQ), and is particularly suited for high-dimensional data with complex dependencies.**

**We used the kmbayes function from the bkmr package to fit the BKMR model. A cover design was used to generate knot points for the model, and posterior inclusion probabilities (PIPs) were extracted to identify significant predictors.**

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**# Extract the response variable (IQ) and the exposure matrix (metals)**

**iq <- cleaned\_data %>% pull(QI)**

**expos <- data.matrix(cleaned\_data %>% select(Cadmium:Manganese))**

**# Generate knot points using a cover design for Bayesian modeling**

**knots50 <- fields::cover.design(expos, nd = 50)$design**

**# Fit the BKMR model using MCMC**

**modelFit <- kmbayes(**

**y = iq, # Response variable**

**Z = expos, # Exposure matrix (metal concentrations)**

**X = NULL, # No additional covariates**

**iter = 10000, # Number of MCMC iterations**

**family = "gaussian", # Gaussian response**

**verbose = TRUE, # Output progress for each iteration**

**varsel = TRUE, # Perform variable selection**

**knots = knots50 # Knot points generated earlier**

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**5. Dynamic Threshold Calculation**

**To assess the relative importance of metal exposures, we calculate a dynamic threshold for variable inclusion. This threshold is based on the coefficient of variation (CV) of the IQ scores and the sample size.**

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**# Calculate the dynamic threshold for model inclusion**

**pipThresh\_fn <- calculate\_pip\_threshold(**

**absCV = sd(cleaned\_data$QI) / mean(cleaned\_data$QI), # Coefficient of variation**

**sampSize = length(cleaned\_data$QI) # Sample size**

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**6. Identification of Significant Exposures**

**We then compare the posterior inclusion probabilities (PIPs) with the dynamic threshold to identify significant metal exposures. Exposures with PIPs greater than the dynamic threshold are considered significant predictors of IQ scores.**

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**# Extract posterior inclusion probabilities (PIPs) and sort them**

**pipFit <- ExtractPIPs(modelFit) %>% arrange(desc(PIP))**

**# Identify exposures with PIPs greater than the threshold**

**significant\_exposures <- pipFit %>% filter(PIP > pipThresh\_fn)**

**5. Discussion**

**The R package we developed is a valuable tool for simulating multivariate environmental exposure data and estimating feature selection thresholds for Bayesian Kernel Machine Regression (BKMR). By supporting multivariate normal and skewed Gamma distributions, the package is particularly well-suited for handling non-normal environmental exposure data, which is common in health studies.**

**While BKMR is an excellent tool for feature selection, its reliance on normality can limit its application to real-world datasets. Our package fills this gap by enabling researchers to model and analyze non-normally distributed data, ensuring that feature selection remains robust even in complex scenarios.**

**6. Conclusion**

**This R package provides essential tools for simulating multivariate environmental exposure data, estimating statistical moments, and calculating PIP thresholds for feature selection in Bayesian Kernel Machine Regression (BKMR). The ability to simulate data from multivariate normal and skewed Gamma distributions makes the package particularly valuable for environmental health studies where data often deviate from normality.**

**This updated version includes the real-world scenario, which uses the Taranto Children Study dataset, fits the Bayesian Kernel Machine Regression (BKMR) model, calculates a dynamic threshold, and identifies significant exposures. Let me know if you need any further adjustments!**

**You said:**

**now write these in details for a scientific journal article and give a .qmd file**

**ChatGPT said:**

**Certainly! Below is a detailed version of the scientific journal article written in the style appropriate for submission, incorporating the necessary methods, software implementation, and real-world scenario. After that, I'll provide the content in Quarto (QMD) format, which can be compiled into a complete scientific article.**

**Title: An R Package for Simulating Multivariate Environmental Exposure Data and Estimating Feature Selection Thresholds for Bayesian Kernel Machine Regression**

**Abstract**

**In environmental health studies, the relationship between multiple environmental exposures and health outcomes, such as cognitive development, is often investigated using complex datasets that exhibit non-normality. This paper introduces an R package designed to simulate multivariate environmental exposure data and estimate feature selection thresholds for Bayesian Kernel Machine Regression (BKMR). The package enables researchers to generate data from multivariate normal and skewed Gamma distributions, common in environmental exposure research, and calculate statistical features such as mean, variance, skewness, and correlation. The package also facilitates the calculation of the Posterior Inclusion Probability (PIP) threshold for feature selection in BKMR, offering an approach that accounts for non-normal data. The effectiveness of the package is demonstrated through a real-world application using data from the Taranto Children Study, where metal exposures are related to IQ scores.**

**Keywords**

**R package, Bayesian Kernel Machine Regression, multivariate simulation, feature selection, environmental exposure, statistical moments, Gamma distribution, skewed Gamma distribution, non-normal data**

**1. Introduction**

**Environmental exposure to metals such as Cadmium, Mercury, Arsenic, and Lead is linked to various adverse health outcomes, especially among children. In particular, these exposures may influence cognitive functions, with effects that often vary based on the concentration of metals in the environment. Research into these relationships frequently involves complex, multivariate datasets where environmental factors are correlated, and data distributions often exhibit skewness rather than normality.**

**The Bayesian Kernel Machine Regression (BKMR) model is a powerful method for identifying relevant environmental factors and interactions. However, its effectiveness is typically constrained by its assumption of normality in the data, which is frequently violated in environmental health studies. To address this limitation, we have developed an R package that facilitates data simulation for multivariate environments and estimates the Posterior Inclusion Probability (PIP) threshold for feature selection within the BKMR framework, particularly when data deviate from normality.**

**This article presents the R package and demonstrates its utility by simulating environmental exposure data from multivariate normal and skewed Gamma distributions, estimating key statistical moments, and applying BKMR to assess the effects of metal exposures on children's IQ scores using real-world data.**

**2. Materials and Methods**

**2.1. Overview of the R Package**

**The package aims to provide a robust framework for simulating non-normal environmental exposure data and estimating feature selection thresholds in the context of Bayesian Kernel Machine Regression (BKMR). The core functions of the package include:**

1. **Data Simulation: Functions for generating multivariate data from Normal, Gamma, and skewed Gamma distributions.**
   * **simulate\_group\_data: Generates data using multivariate normal or Gamma distributions.**
   * **simulate\_group\_gaussian: Specifically generates data from a multivariate normal distribution.**
   * **simulate\_group\_gamma: Generates data from a multivariate Gamma distribution.**
   * **generate\_mvGamma\_data: Generates multivariate skewed Gamma data by transforming multivariate normal samples.**
2. **Statistical Moment Estimation: The function estimate\_mv\_moments calculates key statistical moments, including mean, variance, skewness, and correlation matrix, which are essential for understanding the underlying structure of the data.**
3. **Feature Selection Threshold Calculation: The function calculate\_pip\_threshold estimates the Posterior Inclusion Probability (PIP) threshold using Richard’s Four-Parameter Logistic Regression to ensure robust feature selection in BKMR.**

**2.2. Data Simulation Methods**

**The package provides methods for simulating environmental exposure data that reflect the non-normal nature of environmental health data:**

* **Multivariate Normal Distribution: The simulate\_group\_gaussian function generates multivariate normal data, which can be useful when data are approximately normal.**
* **Multivariate Gamma Distribution: The simulate\_group\_gamma function generates multivariate Gamma-distributed data, which is appropriate for modeling exposure data that are right-skewed, as is typical for metal concentrations.**
* **Multivariate Skewed Gamma Distribution: The generate\_mvGamma\_data function simulates skewed Gamma-distributed data. This is particularly useful in modeling data with significant skewness, common in environmental exposure studies.**

**2.3. Statistical Moment Estimation**

**The estimate\_mv\_moments function is used to compute the following statistical moments for each variable in the dataset:**

* **Sample Size: The number of observations per group.**
* **Mean Vector: The mean for each variable.**
* **Standard Deviation Vector: The standard deviation for each variable.**
* **Skewness: A measure of asymmetry in the data distribution.**
* **Correlation Matrix: A matrix showing the relationships between variables.**

**These statistical moments help characterize the underlying distribution of the data and are critical for performing feature selection in BKMR.**

**2.4. Feature Selection and Threshold Estimation**

**The PIP threshold for feature selection is computed using the calculate\_pip\_threshold function. This function estimates the threshold based on a Four-Parameter Logistic Regression model (Richard’s curve), which adjusts for variations in data and sample size. The formula used to calculate the PIP threshold is:**

**PIP(q95)=A+K−A(C+exp⁡(−β1⋅x1))β2⋅x2PIP(q\_{95}) = A + \frac{K - A}{ (C + \exp(-\beta\_1 \cdot x\_1) )^{\beta\_2 \cdot x\_2} }PIP(q95​)=A+(C+exp(−β1​⋅x1​))β2​⋅x2​K−A​**

**Where:**

* **AAA and KKK are asymptotes, with A=0A = 0A=0 and KKK determined by the data.**
* **β1,β2\beta\_1, \beta\_2β1​,β2​ are parameters that control the midpoint shift for coefficient variation and sample size.**
* **x1x\_1x1​ and x2x\_2x2​ represent the logarithmic transformations of CV and sample size, respectively.**

**2.5. Data Transformation Functions**

**The package includes data transformation functions to prepare data for analysis:**

* **Scaling by Standard Deviation or MAD: The trans\_ratio function scales data by either the standard deviation (SD) or the median absolute deviation (MAD).**
* **Logarithmic and Root Transformations: The trans\_log function applies a logarithmic transformation to the data, and the trans\_root function allows for fractional root transformations, helping to manage skewed data.**

**3. Software Implementation**

**3.1. Installation**

**To install the package from CRAN, use:**

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**install.packages("name\_of\_your\_package")**

**For GitHub installation, use:**

**r**

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**devtools::install\_github("username/name\_of\_your\_package")**

**3.2. Package Functions**

**The key functions of the package include:**

1. **simulate\_group\_gaussian: Generates multivariate normal data.**
2. **simulate\_group\_gamma: Generates multivariate Gamma data.**
3. **generate\_mvGamma\_data: Generates multivariate skewed Gamma data.**
4. **estimate\_mv\_moments: Computes statistical moments (mean, variance, skewness, etc.).**
5. **calculate\_pip\_threshold: Estimates the PIP threshold for feature selection.**

**3.3. Example Usage**

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**# Simulate multivariate normal data**

**param\_list <- list(**

**Group1 = list(mean\_vec = c(1, 2), sampCorr\_mat = matrix(c(1, 0.5, 0.5, 1), 2, 2), sampSize = 100),**

**Group2 = list(mean\_vec = c(2, 3), sampCorr\_mat = matrix(c(1, 0.3, 0.3, 1), 2, 2), sampSize = 150)**

**)**

**simulated\_data <- simulate\_group\_gaussian(param\_list, "Group")**

**# Calculate PIP threshold**

**pip\_threshold <- calculate\_pip\_threshold(y = response\_data, absCV = 0.05, sampSize = 100)**

**4. Real-World Scenario**

**1. Dataset Overview**

**The data used in this study is sourced from the *Taranto Children Study*, which includes information on children's IQ scores, metal concentrations (Cadmium, Mercury, Arsenic, Lead, and Manganese), and gender. The dataset was pre-processed to remove missing values, and only the relevant variables—IQ, metal concentrations, and gender—were retained for analysis.**

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**library(bkmr)**

**library(simBKMRdata)**

**library(tidyverse)**

**# Load the dataset**

**bkmrAnalysisData\_df <- data("metalExposChildren\_df")**

**# Preprocess the data by selecting relevant columns and removing missing values**

**bkmrAnalysisData\_df <- metalExposChildren\_df %>%**

**select(QI, Cadmium:Manganese, Sex) %>%**

**na.omit() %>%**

**mutate(**

**across(Cadmium:Manganese, ~ trans\_log(.))**

**)**

**2. Estimation of Moments for Multivariate Skewed Gamma Distribution**

**To appropriately model the skewed nature of the metal exposure data, we estimate the moments (mean, variance, and skewness) of each metal using a multivariate skewed gamma distribution. This distribution was chosen because metal concentrations often exhibit right skewness and heteroscedasticity, making it a suitable model for these variables.**

**4. Bayesian Kernel Machine Regression (BKMR)**

**Bayesian Kernel Machine Regression (BKMR) was employed to investigate the effects of metal exposures on children's IQ scores. This method allows for non-linear relationships between predictors (metal exposures) and the outcome (IQ), and is particularly suited for high-dimensional data with complex dependencies.**

**We used the kmbayes function from the bkmr package to fit the BKMR model. A cover design was used to generate knot points for the model, and posterior inclusion probabilities (PIPs) were extracted to identify significant predictors.**

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**# Extract the response variable (IQ) and the exposure matrix (metals)**

**iq <- cleaned\_data %>% pull(QI)**

**expos <- data.matrix(cleaned\_data %>% select(Cadmium:Manganese))**

**# Generate knot points using a cover design for Bayesian modeling**

**knots50 <- fields::cover.design(expos, nd = 50)$design**

**# Fit the BKMR model using MCMC**

**modelFit <- kmbayes(**

**y = iq, # Response variable**

**Z = expos, # Exposure matrix (metal concentrations)**

**X = NULL, # No additional covariates**

**iter = 10000, # Number of MCMC iterations**

**family = "gaussian", # Gaussian response**

**verbose = TRUE, # Output progress for each iteration**

**varsel = TRUE, # Perform variable selection**

**knots = knots50 # Knot points generated earlier**

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**5. Dynamic Threshold Calculation**

**To assess the relative importance of metal exposures, we calculate a dynamic threshold for variable inclusion. This threshold is based on the coefficient of variation (CV) of the IQ scores and the sample size.**

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**# Calculate the dynamic threshold for model inclusion**

**pipThresh\_fn <- calculate\_pip\_threshold(**

**absCV = sd(cleaned\_data$QI) / mean(cleaned\_data$QI), # Coefficient of variation**

**sampSize = length(cleaned\_data$QI) # Sample size**

**)**

**6. Identification of Significant Exposures**

**We then compare the posterior inclusion probabilities (PIPs) with the dynamic threshold to identify significant metal exposures. Exposures with PIPs greater than the dynamic threshold are considered significant predictors of IQ scores.**

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**# Extract posterior inclusion probabilities (PIPs) and sort them**

**pipFit <- ExtractPIPs(modelFit) %>% arrange(desc(PIP))**

**# Identify exposures with PIPs greater than the threshold**

**significant\_exposures <- pipFit %>% filter(PIP > pipThresh\_fn)**

**5. Discussion**

**The R package we developed is a valuable tool for simulating multivariate environmental exposure data and estimating feature selection thresholds for Bayesian Kernel Machine Regression (BKMR). By supporting multivariate normal and skewed Gamma distributions, the package is particularly well-suited for handling non-normal environmental exposure data, which is common in health studies.**

**While BKMR is an excellent tool for feature selection, its reliance on normality can limit its application to real-world datasets. Our package fills this gap by enabling researchers to model and analyze non-normally distributed data, ensuring that feature selection remains robust even in complex scenarios.**

**6. Conclusion**

**This R package provides essential tools for simulating multivariate environmental exposure data, estimating statistical moments, and calculating PIP thresholds for feature selection in Bayesian Kernel Machine Regression (BKMR). The ability to simulate data from multivariate normal and skewed Gamma distributions makes the package particularly valuable for environmental health studies where data often deviate from normality.**