Supplementary File 1: Estimation algorithm and algorithm for the null model.

A Estimation algorithm

Here we present the algorithm used for fitting the quantile VMICM model.

Step 1 & 2: The algorithms used in these steps follow directly from Peng and Wang[29]. We implemented these steps using the R package "rqPen"[30].

Step 3: Obtain

$$\widehat{\boldsymbol{\beta}} = \arg \min_{||\boldsymbol{\beta}||_2=1} Q_3(\boldsymbol{\beta} \mid \lambda_3, \widehat{\boldsymbol{\gamma}}^{(2)}),$$

where

$$Q_3(\boldsymbol{\beta} \mid \lambda_3, \widehat{\boldsymbol{\gamma}}) = \sum_{i=1}^{n} \rho_\tau \left(Y_i - \sum_{k=0}^{p} \left[\widehat{\gamma}_{k1} + \bar{\boldsymbol{B}}(\boldsymbol{X}\boldsymbol{\beta})\widehat{\boldsymbol{\gamma}}_{k*} \right] G_{ik} \right) + n \sum_{d=2}^{q} p_{\lambda_3}(|\beta_d|).$$

Since $\bar{\boldsymbol{B}}(\boldsymbol{X}\boldsymbol{\beta})$ is not linear in $\boldsymbol{\beta}$, we adopt a first-order Taylor approximation. Let $\tilde{\boldsymbol{\beta}}$ denote the current estimate of $\boldsymbol{\beta}$. Then

$$\bar{\boldsymbol{B}}(\boldsymbol{X}\boldsymbol{\beta})\widehat{\boldsymbol{\gamma}}_{k*}\boldsymbol{G}_k \approx \bar{\boldsymbol{B}}(\boldsymbol{X}\tilde{\boldsymbol{\beta}})\widehat{\boldsymbol{\gamma}}_{k*}\boldsymbol{G}_k + \bar{\boldsymbol{B}}'(\boldsymbol{X}\tilde{\boldsymbol{\beta}})\widehat{\boldsymbol{\gamma}}_{k*}\boldsymbol{X}\boldsymbol{G}_k(\boldsymbol{\beta} - \tilde{\boldsymbol{\beta}}).$$

For each component β_d, $d = 1, \ldots, q$, we approximate

$$\bar{\boldsymbol{B}}(\boldsymbol{X}\boldsymbol{\beta})\widehat{\boldsymbol{\gamma}}_{k*}\boldsymbol{G}_k \approx \bar{\boldsymbol{B}}(\boldsymbol{X}\tilde{\boldsymbol{\beta}})\widehat{\boldsymbol{\gamma}}_{k*}\boldsymbol{G}_k + \bar{\boldsymbol{B}}'(\boldsymbol{X}\tilde{\boldsymbol{\beta}})\widehat{\boldsymbol{\gamma}}_{k*}\boldsymbol{X}_d\boldsymbol{G}_k(\beta_d - \tilde{\beta}_d).$$

Therefore, $\widehat{\beta}_d$ can be obtained by minimizing

$$Q_d = \sum_{i=1}^{n} \rho_\tau(Y^*_{di} - X^*_{di}\beta_d) + np_{\lambda_3}(|\beta_d|),$$

where

$$\boldsymbol{Y}^*_d = \boldsymbol{Y} - \sum_{k=0}^{p} \left[\widehat{\gamma}_{k1}\boldsymbol{G}_k + \bar{\boldsymbol{B}}(\boldsymbol{X}\tilde{\boldsymbol{\beta}})\widehat{\boldsymbol{\gamma}}_{k*}\boldsymbol{G}_k - \bar{\boldsymbol{B}}'(\boldsymbol{X}\tilde{\boldsymbol{\beta}})\widehat{\boldsymbol{\gamma}}_{k*}\boldsymbol{G}_k\boldsymbol{X}_d\tilde{\beta}_d \right],$$

and

$$\boldsymbol{X}^*_d = \sum_{k=0}^{p} \bar{\boldsymbol{B}}'(\boldsymbol{X}\tilde{\boldsymbol{\beta}})\widehat{\boldsymbol{\gamma}}_{k*}\boldsymbol{G}_k\boldsymbol{X}_d.$$

The MCP-penalized estimator $\widehat{\boldsymbol{\beta}}^* = (\beta^*_1, \ldots, \beta^*_q)^T$ is obtained as follows:

(1) For a given initial value $\tilde{\boldsymbol{\beta}}$, compute $\boldsymbol{Y}^*_d$ and $\boldsymbol{X}^*_d$ according to the above expressions.

(2) Obtain $\widehat{\boldsymbol{\beta}}^*$ by applying an iterative coordinate descent algorithm for penalized quantile regression.

(3) Standardize $\widehat{\boldsymbol{\beta}}^*$ via

$$\widehat{\boldsymbol{\beta}} = \mathrm{sign}(\widehat{\beta}_1^*)\frac{\widehat{\boldsymbol{\beta}}^*}{||\widehat{\boldsymbol{\beta}}^*||_2}.$$

(4) Repeat steps (1)–(3) until convergence.

B Algorithm for the null model

Consider the intercept-only model

$$Y = m_0(\boldsymbol{X\beta}) + \boldsymbol{\epsilon}.$$

We propose the following iterative algorithm for parameter estimation.

(0) Approximate $m_0(\boldsymbol{X\beta})$ using B-spline basis functions:

$$m_0(\boldsymbol{X\beta}) \approx \gamma_{01} + \bar{\boldsymbol{B}}(\boldsymbol{X\beta})\boldsymbol{\gamma}_{0*}.$$

(1) For a given initial value $\widehat{\boldsymbol{\beta}}$, estimate $\widehat{\gamma}_{01}$ and $\widehat{\boldsymbol{\gamma}}_{0*}$ using the "rq" function in R (package "quantreg"), where $\bar{\boldsymbol{B}}(\boldsymbol{X}\widehat{\boldsymbol{\beta}})$ serves as the design matrix.

(2) Update $\boldsymbol{\beta}$ by minimizing

$$\sum_{i=1}^{n} \rho_\tau \left(Y_i - \widehat{\gamma}_{01} - \bar{\boldsymbol{B}}(\boldsymbol{X\beta})\widehat{\boldsymbol{\gamma}}_{0*} \right),$$

using the linear approximation method described above.

(3) Replace $\widehat{\boldsymbol{\beta}}$ with the updated value and iterate steps (1) and (2) until convergence.

References

[1] Falconer DS. 1952. The problem of environment and selection. *The American Naturalist* 86:293–299 http://doi.org/doi.org/10.1086/281736

[2] Ottman R. 1996. Gene-environment interaction: definitions and study designs. *Preventive Medicine* 25(6):764 http://doi.org/10.1006/pmed.1996.0117

[3] Ma S, Yang L, Romero R, and Cui Y. 2011. Varying coefficient model for gene-environment interaction: a non-linear look. *Bioinformatics* 27(15):2119–2126 http://doi.org/10.1093/bioinformatics/btr318

[4] Carpenter DO, Arcaro K, and Spink DC. 2002. Understanding the human health effects of chemical mixtures. *Environmental Health Perspectives* 110(Suppl 1):25 http://doi.org/10.1289/ehp.02110s125

[5] Sexton K and Hattis D. 2007. Assessing cumulative health risks from exposure to environmental mixtures–three fundamental questions. *Environmental Health Perspectives* pages 825–832 http://doi.org/10.1289/ehp.9333

[6] Liu X, Cui Y, and Li R. 2016. Partial linear varying multi-index coefficient model for integrative gene-environment interactions. *Statistica Sinica* 26:1037–1060 http://doi.org/10.5705/ss.202015.0114

[7] Guan S, Zhao M, and Cui Y. 2023. Variable selection for single-index varying-coefficients models with applications to synergistic g$\times$e interactions. *Electronic Journal of Statistics* 17(1):823–857 http://doi.org/10.1214/23-ejs2117

[8] Guan S, Liu X, and Cui Y. 2025. Variable selection for generalized single-index varying-coefficient models with applications to synergistic g$\times$e interactions. *Mathematics* 13(3):469 http://doi.org/10.3390/math13030469

[9] Reyes L and Manalich R. 2005. Long-term consequences of low birth weight. *Kidney International* 68(Suppl 97):S107–S111 http://doi.org/10.1111/j.1523-1755.2005.09718.x

[10] Magnusson A, Laivuori H, Loft A, et al.. 2021. The association between high birth weight and long-term outcomes–implications for assisted reproductive technologies: a systematic review and meta-analysis. *Frontiers in Pediatrics* 9:675775 http://doi.org/10.3389/fped.2021.675775

[11] Fan J and Li R. 2001. Variable selection via nonconcave penalized likelihood and its oracle properties. *Journal of the American Statistical Association* 96(456):1348–1360 http://doi.org/10.1198/016214501753382273

[12] Zhang CH. 2010. Nearly unbiased variable selection under minimax concave penalty. *The Annals of Statistics* 38(2):894–942 http://doi.org/10.1214/09-AOS729

[13] Zou H. 2006. The adaptive lasso and its oracle properties. *Journal of the American Statistical Association* 101(476):1418–1429 http://doi.org/10.1198/016214506000000735

[14] Schumaker L, 2007. *Spline Functions: Basic Theory.* Cambridge University Press.

[15] de Boor C, 2001. *A Practical Guide to Splines.* Springer.

[16] Eilers PHC and Marx BD. 1996. Flexible smoothing with b-splines and penalties. *Statistical Science* 11(2):89–121 http://doi.org/10.1214/ss/1038425655

[17] Ruppert D, Wand MP, and Carroll RJ, 2003. *Semiparametric Regression*. Cambridge University Press.

[18] Tang Y, Wang HJ, Zhu Z, and Song X. 2012. A unified variable selection approach for varying coefficient models. *Statistica Sinica* pages 601–628 http://doi.org/10.5705/ss.2010.121

[19] Wu C, Zhong PS, and Cui Y. 2018. Additive varying-coefficient model for nonlinear gene-environment interactions. *Statistical Applications in Genetics and Molecular Biology* 17(2):20170008 http://doi.org/10.1515/sagmb-2017-0008

[20] Wang L, Wu Y, and Li R. 2012. Quantile regression for analyzing heterogeneity in ultra-high dimension. *Journal of the American Statistical Association* 107(497):214–222 http://doi.org/10.1080/01621459.2012.656014

[21] Schwarz G. 1978. Estimating the dimension of a model. *The Annals of Statistics* 6(2):461–464 http://doi.org/10.1214/aos/1176344136

[22] Galvao AF and Montes-Rojas GV. 2010. Penalized quantile regression for dynamic panel data. *Journal of Statistical Planning and Inference* 140(11):3476–3497 http://doi.org/10.1016/j.jspi.2010.05.008

[23] Lee ER, Noh H, and Park BU. 2014. Model selection via bayesian information criterion for quantile regression models. *Journal of the American Statistical Association* 109(505):216–229 http://doi.org/10.1080/01621459.2013.836975

[24] Fan TC, Yeo HL, Hung TH, Chang NC, Tang YH, Yu J, Chen SH, and Yu AL. 2025. St3gal1 regulates cancer cell migration through crosstalk between egfr and neuropilin-1 signaling. *Journal of Biological Chemistry* 301(4):108368 http://doi.org/10.1016/j.jbc.2025.108368

[25] Horikoshi M, Beaumont RN, Day FR, et al.. 2016. Genome-wide associations for birth weight and correlations with adult disease. *Nature* 538(7624):248–252 http://doi.org/10.1038/nature19806

[26] Ma S and Song PXK. 2015. Varying index coefficient models. *Journal of the American Statistical Association* 110(509):341–356 http://doi.org/10.1080/01621459.2014.903185

[27] Ma S and Xu S. 2015. Semiparametric nonlinear regression for detecting gene and environment interactions. *Journal of Statistical Planning and Inference* 156:31–47 http://doi.org/10.1016/j.jspi.2014.08.005

[28] Belloni A, Chernozhukov V, and Kato K. 2018. Valid post-selection inference in high-dimensional approximately sparse quantile regression models. *Journal of the American Statistical Association* 113(522):749–758 http://doi.org/10.1080/01621459.2018.1442339

[29] Peng B and Wang L. 2015. An iterative coordinate descent algorithm for high-dimensional nonconvex penalized quantile regression. *Journal of Computational and Graphical Statistics* 24(3):676–694 http://doi.org/10.1080/10618600.2014.913516

[30] Sherwood B and Maidman A. 2020. rqpen: Penalized quantile regression. https://cran.r-project.org/web/packages/rqPen/ http://doi.org/10.32614/RJ-2025-017