Semiparametric Bayesian Kernel Survival Model for Evaluating Pathway Effects

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S1 Full Conditional Distributions

$$
\begin{aligned}
p(\boldsymbol{\beta}|-) \quad &\propto \exp\left[\sum_{i=1}^{n}\delta_i \boldsymbol{x}_i{}^T\boldsymbol{\beta} - \sum_{i=1}^{n}\exp\Big\{\boldsymbol{x}_i{}^T\boldsymbol{\beta} + g(\boldsymbol{z}_i)\Big\}t_i - \frac{(\boldsymbol{\beta}-\boldsymbol{\mu}_\beta)^T(\boldsymbol{\beta}-\boldsymbol{\mu}_\beta)}{2\sigma_\beta^2}\right];\\
p\Big[\boldsymbol{g}(z)|-\Big] \quad &\propto \exp\left[\sum_{i=1}^{n}\delta_i g(\boldsymbol{z}_i) - \sum_{i=1}^{n}\exp\Big\{x_i^T\beta + g(\boldsymbol{z}_i)\Big\}t_i - \frac{\boldsymbol{g}(\boldsymbol{z})^T K^{-1}\boldsymbol{g}(\boldsymbol{z})}{2\tau}\right];\\
p(\tau|-) \quad &\propto IG\left\{\mu_\tau + \frac{n}{2}, \quad \nu_\tau\rho + \frac{\boldsymbol{g}(\boldsymbol{z})^T K^{-1}\boldsymbol{g}(\boldsymbol{z})}{2}\right\};\\
p(\rho|-) \quad &\propto |K|^{-\frac{1}{2}}\exp\Big\{-\frac{\boldsymbol{g}(\boldsymbol{z})^T K^{-1}\boldsymbol{g}(\boldsymbol{z})}{2\tau}\Big\}\rho^{\mu_\tau}\exp\Big(-\frac{\rho\nu_\tau}{\tau}\Big)\pi(\rho),
\end{aligned}
$$

where "$-$" means all other terms, and $\pi(\rho)$ is the density function of the prior distribution of ρ.

S2 The List of Simulations Settings

Simulation Setting 1: Correctly specified mechanism of pathway effect, that is, $\boldsymbol{g}(\boldsymbol{z}) \sim MVN\Big[0, \tau K(.,.)\Big]$, where $\tau = 10$,

1.1: $p = 5$, $\gamma = 5/0$, and $\tau/\rho = (0.1, 0.2, 0.5, 2/3, 1, 2, 5, 10)$;

1.2: $p = 50$, $\gamma = 5/45$, and $\tau/\rho = (0.05, 0.1, 0.2, 0.5, 1, 2, 4, 5, 10)$;

1.3: $p = 100$, $\gamma = 10/90$, and $\tau/\rho = (0.025, 0.05, 0.1, 0.2, 0.5, 1, 2, 4, 5, 10)$.

Simulation Setting 2: Unknown mechanism of pathway effect

2.1: $p = 5$, $\gamma = 5/0$, $g(\boldsymbol{z}_i) = \cos(z_{i1}) - 1.5z_{i2}^2 + \exp(-z_{i3})z_{i4} - 0.8\sin(z_{i5})\cos(z_{i3}) + 2z_{i1}z_{i5}$;

2.2: $p = 50$, $\gamma = 5/45$, $g(\boldsymbol{z}_i) = \cos(z_{i1}) - 1.5z_{i2}^2 + \exp(-z_{i3})z_{i4} - 0.8\sin(z_{i5})\cos(z_{i3}) + 2z_{i1}z_{i5}$;

2.3: $p = 100$, $\gamma = 10/90$, $g(\boldsymbol{z}_i) = \cos(z_{i1}) - 1.5z_{i2}^2 + \exp(-z_{i3})z_{i4} - 0.8\sin(z_{i5})\cos(z_{i3}) + 2z_{i1}z_{i5} + 0.9z_{i6}\sin(z_{i7}) - 0.8\cos(z_{i6})z_{i7} + 2z_{i8}\sin(z_{i9})\sin(z_{i10}) - 1.5z_{i8}^3 - z_{i8}z_{i9} - 0.1\exp(z_{i10})\cos(z_{i10})$.

Simulation Setting 3: Misspecified mechanism of pathway effect

3.1: $p = 5$, $\gamma = 5/0$, $\boldsymbol{z}_i^* = (z_{i1}, \ldots, z_{i5})$, $g(\boldsymbol{z}_i) = (\boldsymbol{z}_i^{*T}\boldsymbol{z}_i{}^* + 1)^3$;

3.2: $p = 50$, $\gamma = 5/45$, $\boldsymbol{z}_i^* = (z_{i1}, \ldots, z_{i5})$, $g(\boldsymbol{z}_i) = (\boldsymbol{z}_i^{*T}\boldsymbol{z}_i{}^* + 1)^3$;

3.3: $p = 100$, $\gamma = 10/90$, $\boldsymbol{z}_i^* = (z_{i1}, \ldots, z_{i10})$, $g(\boldsymbol{z}_i) = (\boldsymbol{z}_i^{*T}\boldsymbol{z}_i{}^* + 1)^3$.

Simulation Setting 4: Decision Rule - multiple pathways with unknown mechanism

4: Gene expression data were simulated using the *simulator* function [Dettling, 2004] to maintain the correlation structures among gene expressions in breast cancer data set [Pang et al., 2010], and same non-parametric functions were used for $g(\boldsymbol{z}_i)$ as in Simulation Setting 2 for "significant" pathways, with $g(\boldsymbol{z}_i)$ set to 0 for "insignificant" pathways.

Simulation Setting 5: Misspecified the underlying distribution of survival times

5: Same settings as in Simulation Setting 2, but the survival time is simulated from both the lognormal and Weibull distributions.

Each of the simulation settings is discussed further in the following sections. Note that, for Simulation Settings 2.1–3.3, the corresponding settings under H_0 are obtained by setting $g(\boldsymbol{z}_i) = 0$ for $i = 1, \ldots, n$.

S3 Empirical Properties of the τ/ρ Ratio

In this section, we investigated the empirical properties of the τ/ρ ratio through intensive simulation studies. The findings can serve as general guidance to selecting both τ and ρ in GP related problems in the future. For Simulation Settings 1.1–1.3, we fixed τ as 10 and allowed ρ to take different values, resulting in different τ/ρ ratios ranging from 0 to 10. Moreover, the gene-pathway effects were simulated from MVN, indicating that we were

testing whether our s-BKSurv framework would perform well if the data were simulated from the model.

We examined the estimation accuracy for unknown components in terms of mean absolute percentage error (MAPE). The MAPEs are summarized in Supplementary Material Table S1. These results suggest that, when $n > p$, our approach can estimate parameters quite well, with close to 100% coverage probability for credible intervals. The MAPEs for τ were generally higher than the MAPEs for ρ across all values of ρ, as displayed in Supplementary Material Figure S1 and Supplementary Material Figure S2. However, the MAPEs for τ stayed in a narrow range (0.28–0.36), while the MAPEs for ρ increased by a larger magnitude as ρ decreased; that is, MAPE =0.008 when $\rho = 100$ and MAPE = 0.306 when $\rho = 1$. This may be because as ρ decreases, any given $\boldsymbol{z}_i$ tends to have no impact outside of its close neighborhood, and resulting in a very sparse $K(.,.)$ with diagonal elements equal to 1. If this happens, then the covariance of $\boldsymbol{g}(\boldsymbol{z})$ is mainly controlled by τ, so that the data are less informative about ρ. This finding is consistent with our claims in Section 2.2.

Furthermore, the results in Table S1 in the Supplementary Material give us the guidelines for selecting hyperparameters for τ and ρ. A better prior distribution of ρ will not have a large density at extreme values, especially at extremely large values. Given ρ, a better prior density of π should not be concentrated around small values of ρ, i.e., ν_τ/μ_τ should not be too small. Similar results are also described in Table S2 in the Supplementary Material. In addition, the results from Table S3 in the Supplementary Material suggest that when ρ is very large and the τ/ρ ratio is very small, the model's performance in estimating τ will not be satisfactory in the presence of large number of noise genes when $p \gg n$. This finding is reasonable because, as we discussed in Section 2.2, when ρ is very large, noise genes will also have high impact at any given data point, which will compromise the model's ability to correctly estimate unknown parameters.

S4 Goodness-of-fit Test for the Breast Cancer Data

To check the validity of using the proposed s-BKSurv model framework for the survival time of breast cancer patients, we used the simulation-based supremum-type goodness-of-fit test proposed by Li & Sun [Li and Sun, 2000]. The observed test statistics is equal to 6.32, which is less than the critical value (= 10.45) at a 95% significance level (Supplementary Material Figure S3a). This suggests that the survival times come from an exponential distribution. Moreover, following Li & Sun's Li and Sun [2000] suggestions, we obtained Supplementary Material Figure S3b to further check the adequacy of the distribution assumption for survival time by comparing the observed test process with a set of simulated realizations of an approximating process. The solid line representing the observed test process falls within the range of 100 simulated reference paths (dashed lines), which suggests that there is no evidence against the assumption that the survival time is exponentially distributed.

References

Marcel Dettling. Bagboosting for tumor classification with gene expression data. *Bioinformatics*, 20(18):3583–3593, 2004.

Gang Li and Yanqing Sun. A simulation-based goodness-of-fit test for survival data. *Stat Probab Lett*, 47(4):403–410, 2000.

Herbert Pang, Debayan Datta, and Hongyu Zhao. Pathway analysis using random forests with bivariate node-split for survival outcomes. *Bioinformatics*, 26(2):250–258, 2010.

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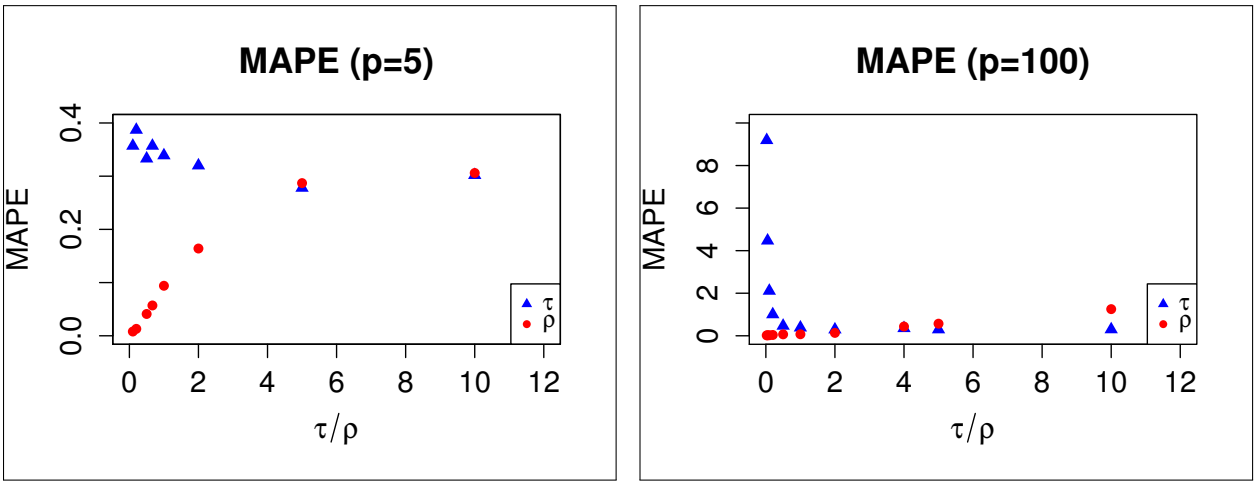


(a) Simulation Setting 1.1.

(b) Simulation Setting 1.3.

Figure S1: Mean Percentage Percentage Error (MAPE) of ρ & τ, respectively. The x-axis represents τ/ρ ratio. The triangles and solid dots represent the MAPE for τ and ρ at different τ/ρ ratios, respectively. The results are based on 100 simulated data sets. Left (a): for Simulation Setting 1.1 ($p < n$), As the ratio goes up from 0.1 to 5, the MAPE for ρ increases rapidly (0.8%–28.7%); the rate of change is getting smaller when ratio is in the range from 5 to 10 (28.7%–30.6%). The MAPE for τ does not have a monotone decreasing trend, and the magnitude of changes is not as dramatical as ρ (38.7% – 28.7%) when the ratio getting larger. Right (b): for Simulation Setting 1.3 ($p \gg n$), as the τ/ρ ratio goes up from 0.025 to 10, the MAPE for ρ increases monotonically from 2.1% to 125.2%. The MAPE for τ does not have a monotone decreasing trend, but the magnitude of changes is more dramatical than ρ (919.1% – 29.2%) when the ratio getting larger.

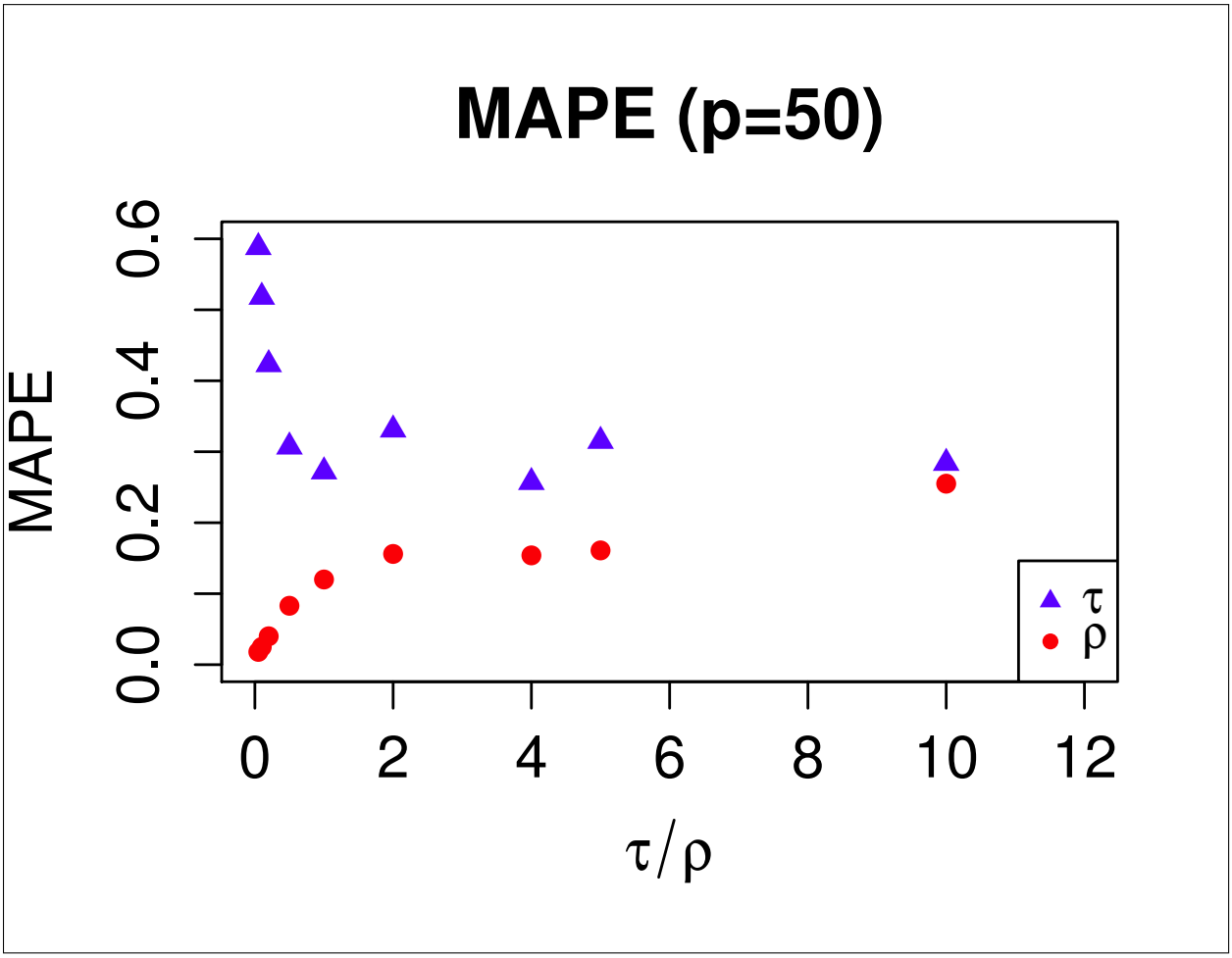
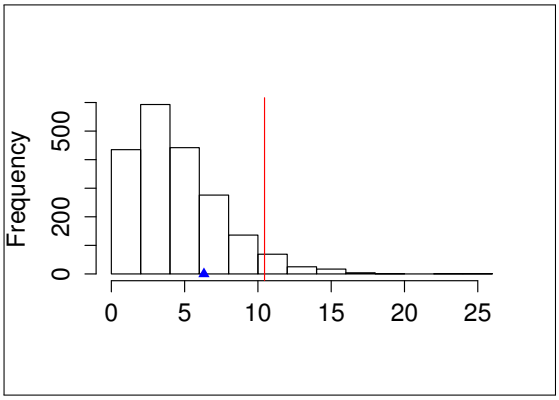
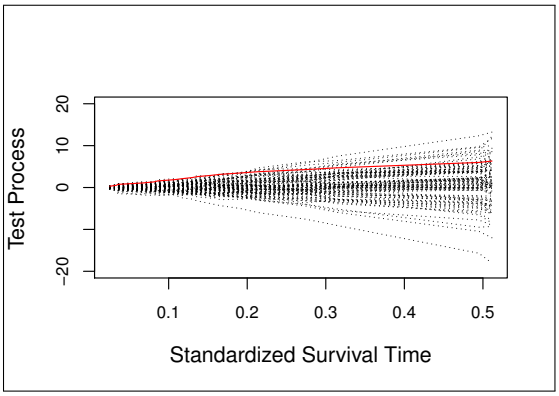


Figure S2: Mean Percentage Percentage Error (MAPE) of ρ & τ, respectively, for p=50 case. The x-axis is the ratio of τ/ρ. The triangles and solid dots represent the MAPE for τ and ρ at different τ/ρ ratios, respectively. The results are based on 100 simulated data sets. As the ratio goes up from 0.05 to 2, the MAPE for *rho* increases rapidly (1.8%–15.6%); the rate of change is getting smaller when ratio is in the range from 2 to 10 (15.6%–25.5%). The MAPE for τ does not have a monotone decreasing trend, and the magnitude of changes is not as dramatical as ρ (58.8% – 25.7%) when the ratio getting larger.

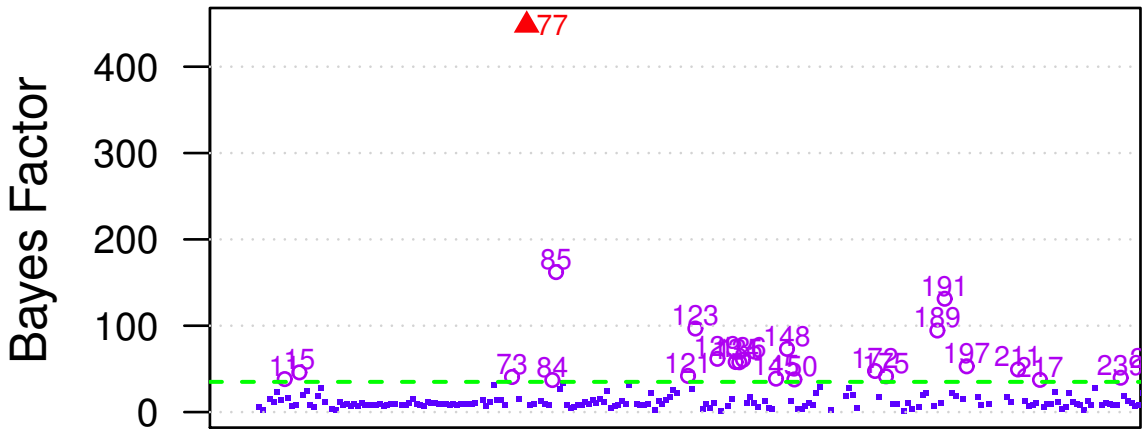


(a) Simulation-based goodness-of-fit test for the Breast Cancer Data–Test Statistics & Critical Value

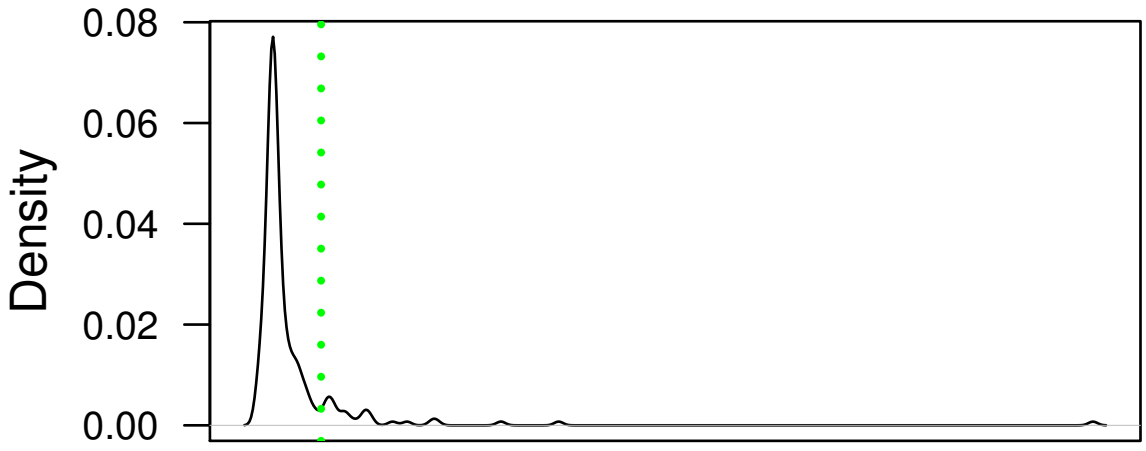


(b) Simulation-based goodness-of-fit test for the Breast Cancer Data–Graphical Tool.

Figure S3: Simulation-based goodness-of-fit test for the breast cancer data. Upper-left (a): Test Statistics & Critical Value. The histogram represents the value for statistics from approximate limiting test processes. The vertical line is the critical value at 95% significant level, and the triangle is the observed test process. Upper-right (b): Graphical Tool. The x-axis is the standardized survival time. The dashed lines are 100 realizations of the approximate limiting test process under the null hypothesis; the solid line is the observed test process calculated from the breast cancer data. By visualizing them, it is easy to tell that the observed test process is within the random number of 100 realizations of the approximate limiting test process under null hypothesis, i.e. the survival time follow exponential distribution.



(a) Bayes Factor Values.



(b) Bayes Factor Density.

Figure S4: Bayes factors (BF) calculated for each pathway in breast cancer data set. (a) The Bayes factors for all 226 pathways. 27 significant pathways based on $BF > 35$ (the dashed line) are marked by their assigned pathway IDs in the data set; (b) The density of Bayes factors for all 226 pathways. Dashed line represents the chosen threshold (i.e. 35).

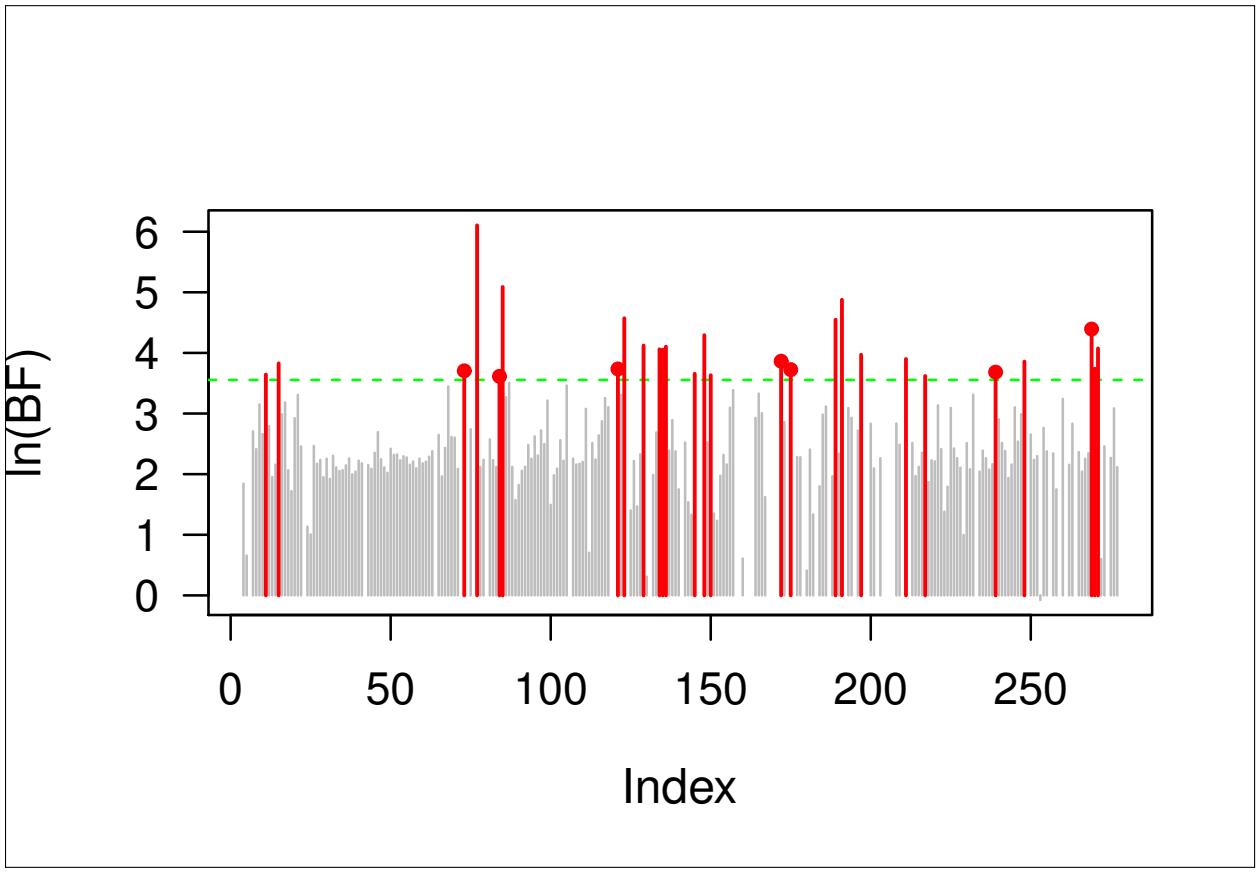


Figure S5: Line plot of Bayes factors from s-BKSurv and p-values from GM2005 after FDR adjustment. The bold lines represent the pathways the are identified as significant pathways (BF $>$ 35) by s-BKSurv; the light lines represent the pathways the are identified as insignificant by s-BKSurv; The bold lines with solid dots represent the pathways that are identified as significant pathways by s-BKSurv but as insignificant pathways by GM2005 (i.e. BF $>$ 35 but p-value $\geq$ 0.05 after FDR adjustment.)

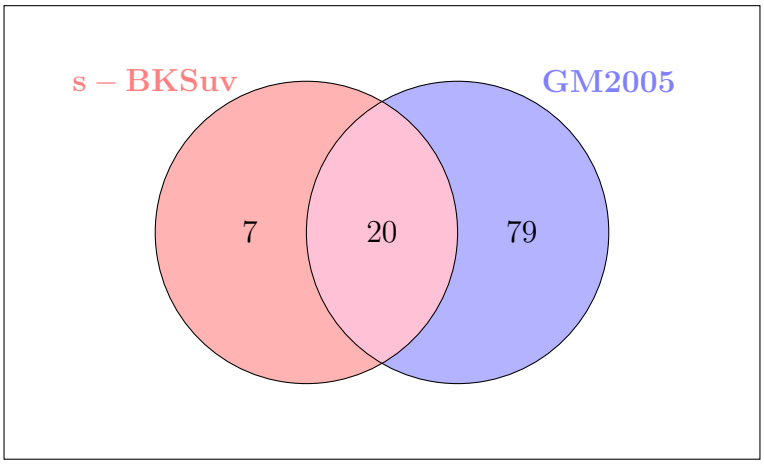


Figure S6: Venn Diagram for the testing results of differentially-expressed pathways. Different circles represent significant pathways using different methods. The left circle (s-BKSurv) represents significant pathways identified by s-BKSurv (total # = 20+7=27); the right circle (GM2005) represents significant pathways identified by GM2005 (total # = 20+79=99); the intersect represents the 9 significant pathways identified by both s-BKSurv and GM2005.

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Table S1: Estimation results for parameters β, τ, and ρ when kernel is correctly specified. All results are based on 100 simulated data sets (Simulation Setting 1.1: $\boldsymbol{g}(\boldsymbol{z}) \sim MVN\Big[0, \tau K(.,.)\Big]$, where $\tau = 10$, $p = 5$, $\gamma = 5/0$, $\tau/\rho = (0.1, 0.2, 0.5, 2/3, 1, 2, 5, 10)$). From left to right, $\frac{\tau}{\rho}$ represents the different τ & ρ ratios; "Parameter" shows the unknown parameters; "True" represents the true values for each unknown parameters under this specific simulation setting; "Estimation" shows corresponding estimated value for each unknown parameter; "S.E." is the standard error for each estimate; "LB & UB" are the lower bound and upper bound of credible intervals, respectively; "%Cover" shows the percentage of credible intervals that covers the true value of each parameter; "MAPE" represents the "mean absolute percentage error", $MAPE = |(Est. - True)/True| * 100$.

$\frac{\tau}{\rho}$	Parameter	True	Estimation	S.E.	C.I.		%Cover	MAPE
					LB	UB		
0.1	β	1.5	1.503	0.450	0.621	2.399	100	0.112
	τ	10	6.093	5.777	2.017	24.273	100	0.357
	ρ	100	99.473	9.881	81.349	120.132	100	0.008
0.2	β	1.5	1.502	0.459	0.624	2.386	100	0.099
	τ	10	6.117	5.066	2.203	21.187	100	0.387
	ρ	50	49.631	7.010	37.208	64.772	100	0.013
0.5	β	1.5	1.474	0.459	0.590	2.359	100	0.100
	τ	10	7.094	5.590	2.635	23.415	98.90	0.333
	ρ	20	19.430	4.352	12.235	29.268	100	0.041
2/3	β	1.5	1.530	0.461	0.621	2.426	100	0.113
	τ	10	6.083	4.981	2.319	20.903	98	0.357
	ρ	15	14.576	3.760	8.465	23.167	100	0.057
1	β	1.5	1.505	0.465	0.602	2.419	100	0.117
	τ	10	6.907	5.027	2.715	21.760	98.98	0.339
	ρ	10	9.301	2.879	4.850	16.080	100	0.094
2	β	1.5	1.504	0.473	0.577	2.432	100	0.096
	τ	10	7.081	4.944	2.911	21.010	96.90	0.320
	ρ	5	4.457	1.907	1.941	9.338	100	0.164
5	β	1.5	1.479	0.481	0.549	2.421	100	0.080
	τ	10	8.150	4.350	3.771	19.860	100	0.278
	ρ	2	1.600	0.782	0.660	3.737	93.9	0.287
10	β	1.5	1.475	0.487	0.522	2.434	100	0.072
	τ	10	8.822	4.273	4.413	20.319	96.97	0.302
	ρ	1	0.794	0.389	0.272	1.801	94.85	0.306

Table S2: Estimation results for parameters β, τ, and ρ when kernel is correctly specified. All results are based on 100 simulated data sets (Simulation Setting 1.2: $\boldsymbol{g}(\boldsymbol{z}) \sim MVN\Big[0, \tau K(.,.)\Big]$, where $\tau = 10$, $p = 50$, $\gamma = 5/45$, $\tau/\rho = (0.05, 0.1, 0.2, 0.5, 1, 2, 4, 5, 10)$). From left to right, $\frac{\tau}{\rho}$ represents the different τ & ρ ratios; "Parameter" shows the unknown parameters; "True" represents the true values for each unknown parameters under this specific simulation setting; "Estimation" shows corresponding estimated value for each unknown parameter; "S.E." is the standard error for each estimate; "LB & UB" are the lower bound and upper bound of credible intervals, respectively; "%Cover" shows the percentage of credible intervals that covers the true value of each parameter; "MAPE" represents the "mean absolute percentage error", $MAPE = |(Est. - True)/True| * 100$.

$\frac{\tau}{\rho}$	Parameter	True	Estimation	S.E.	C.I.		%Cover	MAPE
					LB	UB		
0.05	β	1.5	1.543	0.465	0.632	2.437	100	0.126
	τ	10	4.223	4.585	0.961	18.099	75	0.588
	ρ	200	198.741	12.069	174.805	222.009	100	0.018
0.1	β	1.5	1.498	0.473	0.569	2.436	100	0.111
	τ	10	6.770	4.330	2.113	18.919	85	0.518
	ρ	100	98.616	9.484	80.815	116.915	100	0.025
0.2	β	1.5	1.489	0.483	0.539	2.434	100	0.081
	τ	10	7.692	4.070	2.932	17.848	88	0.423
	ρ	50	48.103	6.668	36.252	62.170	100	0.040
0.5	β	1.5	1.488	0.489	0.527	2.446	100	0.062
	τ	10	9.709	4.131	4.725	20.740	95	0.307
	ρ	20	18.403	4.007	11.697	27.751	100	0.083
1	β	1.5	1.464	0.492	0.505	2.433	100	0.059
	τ	10	9.584	3.641	5.021	19.058	93	0.272
	ρ	10	9.077	2.709	4.849	15.582	100	0.120
2	β	1.5	1.469	0.490	0.507	2.434	100	0.063
	τ	10	10.602	3.856	5.795	20.444	89	0.331
	ρ	5	4.379	1.904	1.580	9.011	100	0.156
4	β	1.5	1.471	0.489	0.514	2.428	100	0.058
	τ	10	9.752	3.615	5.399	19.141	93	0.257
	ρ	2.5	2.142	1.448	0.418	5.927	100	0.154
5	β	1.5	1.444	0.488	0.494	2.407	100	0.064
	τ	10	10.417	3.524	5.733	19.374	93	0.315
	ρ	2	1.662	1.317	0.253	5.219	100	0.161
10	β	1.5	1.413	0.489	0.452	2.378	100	0.076
	τ	10	10.204	3.669	5.603	19.990	96	0.284
	ρ	1	0.733	0.988	0.043	3.696	100	0.255

Table S3: Estimation results for parameters β, τ, and ρ based on 100 simulated data sets (Simulation Setting 1.3: $\boldsymbol{g}(\boldsymbol{z}) \sim MVN\Big[0,\, \tau K(.,.)\Big]$, where $\tau = 10$, $p = 100$, $\gamma = 10/90$, $\tau/\rho = (0.025, 0.05, 0.1, 0.2, 0.5, 1, 2, 4, 5, 10)$). From left to right, τ/ρ represents the different τ & ρ ratios; "Parameter" shows the unknown parameters; "True" represents the true value of each unknown parameter under this specific simulation setting; "Estimation" shows corresponding estimated value of each unknown parameter; "S.E." is the standard error of each estimate; "LB & UB" are the lower bound and upper bound for the credible intervals, respectively; "%Cover" shows the percentage of credible intervals that covers the true values of parameters; "MAPE" represents the "mean absolute percentage error", $MAPE = |(Est. - True)/True| * 100$.

$\frac{\tau}{\rho}$	Parameter	True	Estimation	S.E.	C.I.		%Cover	MAPE
					LB	UB		
0.025	β	1.5	1.492	0.491	0.526	2.452	100	0.037
	τ	10	99.702	32.717	58.536	185.505	0	9.191
	ρ	400	399.765	17.398	368.596	434.071	100	0.021
0.05	β	1.5	1.496	0.493	0.534	2.463	100	0.036
	τ	10	53.639	18.101	31.164	100.282	0	4.470
	ρ	200	199.790	12.919	175.069	225.690	100	0.023
0.1	β	1.5	1.506	0.493	0.542	2.470	100	0.040
	τ	10	30.488	10.638	17.307	58.623	0	2.110
	ρ	100	97.987	9.619	80.367	117.537	100	0.026
0.2	β	1.5	1.492	0.493	0.530	2.460	100	0.040
	τ	10	20.015	7.239	10.986	38.693	36	1.005
	ρ	50	48.130	6.894	36.137	62.753	100	0.038
0.5	β	1.5	1.462	0.494	0.500	2.433	100	0.047
	τ	10	14.009	4.860	7.626	26.733	81	0.467
	ρ	20	18.814	4.053	12.003	28.144	100	0.067
1	β	1.5	1.483	0.491	0.527	2.448	100	0.044
	τ	10	13.028	4.518	7.303	24.303	89	0.383
	ρ	10	9.986	2.957	5.306	16.888	100	0.072
2	β	1.5	1.462	0.488	0.500	2.418	100	0.063
	τ	10	11.457	3.845	6.405	21.494	93	0.292
	ρ	5	5.645	2.191	2.361	10.850	99	0.136
4	β	1.5	1.444	0.489	0.484	2.396	100	0.068
	τ	10	11.615	4.090	6.455	22.478	87	0.355
	ρ	2.5	3.616	1.793	1.184	8.108	100	0.436
5	β	1.5	1.432	0.488	0.474	2.391	100	0.064
	τ	10	11.077	3.948	6.200	21.310	95	0.297
	ρ	2	3.157	1.693	0.938	7.472	100	0.569
10	β	1.5	1.443	0.488	0.489	2.398	100	0.069
	τ	10	9.839	3.662	5.210	19.166	92	0.299
	ρ	1	2.264	1.464	0.542	6.127	100	1.252

Table S4: Hypothesis testing results when pathway effects are simulated via a non-parametric function. Hypothesis testing results for Simulation Setting 2.1 ($p = 5$, $\gamma = 5/0$, $g(\boldsymbol{z}_i) = \cos(z_{i1}) - 1.5z_{i2}^2 + \exp(-z_{i3})z_{i4} - 0.8\sin(z_{i5})\cos(z_{i3}) + 2z_{i1}z_{i5}$). Let TPR denote true positive rate, FPR denote false positive rate, FP denote False Positive, TP denote True Positive, FN denote False Negative, and TN denote True Negative. Then $TPR = \frac{TP}{TP+FN}$, $FPR = \frac{FP}{TN+FP}$, $Accuracy = \frac{TP+TN}{TP+FP+TN+FN}$, $Precision = \frac{TP}{TP+FP}$. BF denotes Bayes Factor. Different numbers in "Prior" are corresponding to different priors.

p	Criteria	Prior	Decision Rule				
			$BF > 1$	$BF > 3$	$BF > 5$	$BF > 10$	$BF > 20$
5	TPR	1)	0.990	0.990	0.970	0.970	0.950
		2)	0.990	0.980	0.980	0.970	0.940
		3)	0.990	0.980	0.980	0.970	0.970
		4)	0.950	0.430	0.370	0.320	0.270
		5)	0.990	0.950	0.920	0.870	0.790
		6)	0.970	0.940	0.920	0.860	0.780
		GM2005: 0.67 (p-value<0.05)					
	FPR	1)	0.150	0.070	0.060	0.060	0.040
		2)	0.200	0.100	0.080	0.060	0.040
		3)	0.440	0.150	0.130	0.100	0.030
		4)	0.470	0.000	0.000	0.000	0.000
		5)	0.140	0.010	0.000	0.000	0.000
		6)	0.110	0.010	0.010	0.000	0.000
		GM2005: 0.03 (p-value<0.05)					
	Accuracy	1)	0.920	0.960	0.955	0.955	0.955
		2)	0.895	0.940	0.950	0.955	0.950
		3)	0.775	0.915	0.925	0.935	0.970
		4)	0.740	0.715	0.685	0.660	0.635
		5)	0.925	0.970	0.960	0.935	0.895
		6)	0.930	0.965	0.955	0.930	0.890
		GM2005: 0.82 (p-value<0.05)					
	Precision	1)	0.868	0.934	0.942	0.942	0.960
		2)	0.832	0.907	0.925	0.942	0.959
		3)	0.692	0.867	0.883	0.907	0.970
		4)	0.669	1.000	1.000	1.000	1.000
		5)	0.876	0.990	1.000	1.000	1.000
		6)	0.898	0.989	0.989	1.000	1.000
		GM2005: 0.957 (p-value<0.05)					

Table S5: Hypothesis testing results when pathway effects are simulated via a non-parametric function. Hypothesis testing results for Simulation Setting 2.2 ($p = 50$, $\gamma = 5/45$, $g(\boldsymbol{z}_i) = \cos(z_{i1}) - 1.5z_{i2}^2 + \exp(-z_{i3})z_{i4} - 0.8\sin(z_{i5})\cos(z_{i3}) + 2z_{i1}z_{i5}$). Let TPR denote true positive rate, FPR denote false positive rate, FP denote False Positive, TP denote True Positive, FN denote False Negative, and TN denote True Negative. Then $TPR = \frac{TP}{TP+FN}$, $FPR = \frac{FP}{TN+FP}$, $Accuracy = \frac{TP+TN}{TP+FP+TN+FN}$, $Precision = \frac{TP}{TP+FP}$. BF denotes Bayes Factor. Different numbers in "Prior" are corresponding to different priors.

p	Criteria	Prior	Decision Rule				
			$BF > 1$	$BF > 3$	$BF > 5$	$BF > 10$	$BF > 20$
50	TPR	1)	1.000	0.980	0.970	0.950	0.950
		2)	0.980	0.970	0.960	0.950	0.940
		3)	1.000	0.990	0.970	0.960	0.940
		4)	0.980	0.920	0.900	0.840	0.750
		5)	0.990	0.690	0.600	0.540	0.490
		6)	1.000	0.990	0.980	0.970	0.970
		7)	0.980	0.970	0.970	0.950	0.950
		GM2005: 0.19 (p-value<0.05)					
	FPR	1)	0.380	0.320	0.280	0.260	0.190
		2)	0.400	0.320	0.290	0.270	0.220
		3)	0.400	0.340	0.300	0.260	0.240
		4)	0.530	0.070	0.030	0.010	0.000
		5)	0.540	0.000	0.000	0.000	0.000
		6)	0.420	0.310	0.280	0.220	0.190
		7)	0.440	0.310	0.250	0.200	0.170
		GM2005: 0.07 (p-value<0.05)					
	Accuracy	1)	0.810	0.830	0.845	0.845	0.880
		2)	0.790	0.825	0.835	0.840	0.860
		3)	0.800	0.825	0.835	0.850	0.850
		4)	0.725	0.925	0.935	0.915	0.875
		5)	0.725	0.845	0.800	0.770	0.745
		6)	0.790	0.840	0.850	0.875	0.890
		7)	0.770	0.830	0.860	0.875	0.890
		GM2005: 0.56 (p-value<0.05)					
	Precision	1)	0.725	0.754	0.776	0.785	0.833
		2)	0.710	0.752	0.768	0.779	0.810
		3)	0.714	0.744	0.764	0.787	0.797
		4)	0.649	0.929	0.968	0.988	1.000
		5)	0.647	1.000	1.000	1.000	1.000
		6)	0.704	0.762	0.778	0.815	0.836
		7)	0.690	0.758	0.795	0.826	0.848
		GM2005: 0.731 (p-value<0.05)					

Table S6: Hypothesis testing results when pathway effects are simulated via a non-parametric function. Hypothesis testing results for Simulation Setting 2.3 ($p = 100$, $\gamma = 10/90$, $g(\boldsymbol{z}_i) = \cos(z_{i1}) - 1.5z_{i2}^2 + \exp(-z_{i3})z_{i4} - 0.8\sin(z_{i5})\cos(z_{i3}) + 2z_{i1}z_{i5} + 0.9z_{i6}\sin(z_{i7}) - 0.8\cos(z_{i6})z_{i7} + 2z_{i8}\sin(z_{i9})\sin(z_{i10}) - 1.5z_{i8}^3 - z_{i8}z_{i9} - 0.1\exp(z_{i10})\cos(z_{i10}))$. Let TPR denote true positive rate, FPR denote false positive rate, FP denote False Positive, TP denote True Positive, FN denote False Negative, and TN denote True Negative. Then $TPR = \frac{TP}{TP+FN}$, $FPR = \frac{FP}{TN+FP}$, $Accuracy = \frac{TP+TN}{TP+FP+TN+FN}$, $Precision = \frac{TP}{TP+FP}$. BF denotes Bayes Factor. Different numbers in "Prior" are corresponding to different priors.

p	Criteria	Prior	Decision Rule				
			$BF > 1$	$BF > 3$	$BF > 5$	$BF > 10$	$BF > 20$
100	TPR	1)	1.000	1.000	1.000	1.000	1.000
		2)	1.000	1.000	1.000	1.000	1.000
		3)	1.000	1.000	1.000	1.000	1.000
		4)	1.000	1.000	1.000	1.000	1.000
		5)	1.000	1.000	1.000	1.000	1.000
		6)	1.000	1.000	1.000	1.000	1.000
		7)	1.000	1.000	1.000	1.000	1.000
		GM2005: 0.16 (p-value<0.05)					
	FPR	1)	0.460	0.370	0.330	0.290	0.250
		2)	0.500	0.430	0.380	0.300	0.220
		3)	0.590	0.120	0.030	0.020	0.000
		4)	0.530	0.420	0.360	0.290	0.250
		5)	0.500	0.380	0.320	0.260	0.230
		6)	0.480	0.390	0.370	0.300	0.260
		7)	0.550	0.420	0.390	0.320	0.280
		GM2005: 0.06 (p-value<0.05)					
	Accuracy	1)	0.751	0.797	0.817	0.838	0.858
		2)	0.731	0.766	0.792	0.832	0.873
		3)	0.685	0.924	0.970	0.975	0.985
		4)	0.716	0.772	0.802	0.838	0.858
		5)	0.731	0.792	0.822	0.853	0.868
		6)	0.741	0.787	0.797	0.832	0.853
		7)	0.706	0.772	0.787	0.822	0.843
		GM2005: 0.55 (p-value<0.05)					
	Precision	1)	0.678	0.724	0.746	0.770	0.795
		2)	0.660	0.693	0.719	0.764	0.815
		3)	0.622	0.890	0.970	0.980	1.000
		4)	0.647	0.698	0.729	0.770	0.795
		5)	0.660	0.719	0.752	0.789	0.808
		6)	0.669	0.713	0.724	0.764	0.789
		7)	0.638	0.698	0.713	0.752	0.776
		GM2005: 0.727 (p-value<0.05)					

Table S7: Hypothesis testing results when kernel is mis-specified. Hypothesis Testing results are summarized for Simulation Setting 3.1 ($p = 5$, $\gamma = 5/0$, $\boldsymbol{z}_i^* = (z_{i1}, \ldots, z_{i5})$). Let TPR denote true positive rate, FPR denote false positive rate, FP denote False Positive, TP denote True Positive, FN denote False Negative, and TN denote True Negative. Then $TPR = \frac{TP}{TP+FN}$, $FPR = \frac{FP}{TN+FP}$, $Accuracy = \frac{TP+TN}{TP+FP+TN+FN}$, $Precision = \frac{TP}{TP+FP}$. BF denotes Bayes Factor. Different numbers in "Prior" are corresponding to different priors.

p	Criteria	Prior	Decision Rule				
			$BF > 1$	$BF > 3$	$BF > 5$	$BF > 10$	$BF > 20$
5	TPR	1)	0.977	0.898	0.875	0.875	0.841
		2)	0.943	0.886	0.886	0.886	0.875
		3)	0.966	0.92	0.909	0.886	0.886
		4)	0.955	0.886	0.875	0.875	0.852
		5)	0.943	0.909	0.898	0.886	0.864
		6)	0.955	0.932	0.920	0.909	0.886
		GM2005: 0.15 (p-value<0.05)					
	FPR	1)	0.190	0.010	0.000	0.000	0.000
		2)	0.080	0.010	0.010	0.000	0.000
		3)	0.060	0.010	0.010	0.010	0.000
		4)	0.180	0.000	0.000	0.000	0.000
		5)	0.090	0.020	0.010	0.000	0.000
		6)	0.070	0.020	0.010	0.000	0.000
		GM2005: 0.04 (p-value<0.05)					
	Accuracy	1)	0.824	0.883	0.878	0.878	0.862
		2)	0.867	0.878	0.878	0.883	0.878
		3)	0.888	0.894	0.888	0.878	0.883
		4)	0.819	0.883	0.878	0.878	0.867
		5)	0.862	0.883	0.883	0.883	0.872
		6)	0.878	0.894	0.894	0.894	0.883
		GM2005: 0.555 (p-value<0.05)					
	Precision	1)	0.819	0.988	1.000	1.000	1.000
		2)	0.912	0.987	0.987	1.000	1.000
		3)	0.934	0.988	0.988	0.987	1.000
		4)	0.824	1.000	1.000	1.000	1.000
		5)	0.902	0.976	0.988	1.000	1.000
		6)	0.923	0.976	0.988	1.000	1.000
		GM2005: 0.789 (p-value<0.05)					

Table S8: Hypothesis testing results when kernel is mis-specified. Hypothesis Testing results are summarized for Simulation Setting 3.2 ($p = 50$, $\gamma = 5/45$, $\boldsymbol{z}_i^* = (z_{i1}, \ldots, z_{i5})$). Let TPR denote true positive rate, FPR denote false positive rate, FP denote False Positive, TP denote True Positive, FN denote False Negative, and TN denote True Negative. Then $TPR = \frac{TP}{TP+FN}$, $FPR = \frac{FP}{TN+FP}$, $Accuracy = \frac{TP+TN}{TP+FP+TN+FN}$, $Precision = \frac{TP}{TP+FP}$. BF denotes Bayes Factor. Different numbers in "Prior" are corresponding to different priors.

p	Criteria	Prior	Decision Rule				
			$BF > 1$	$BF > 3$	$BF > 5$	$BF > 10$	$BF > 20$
50	TPR	1)	0.978	0.846	0.846	0.835	0.813
		2)	0.945	0.923	0.923	0.912	0.890
		3)	0.956	0.923	0.912	0.901	0.868
		4)	0.945	0.846	0.846.	0.824	0.813
		5)	0.945	0.923	0.912	0.901	0.890
		6)	0.956	0.923	0.923	0.912	0.879
		GM2005: 0.10 (p-value<0.05)					
	FPR	1)	0.380	0.010	0.000	0.000	0.000
		2)	0.190	0.030	0.020	0.000	0.000
		3)	0.150	0.030	0.020	0.020	0.010
		4)	0.370	0.000	0.000	0.000	0.000
		5)	0.130	0.020	0.010	0.010	0.010
		6)	0.240	0.020	0.020	0.010	0.010
		GM2005: 0.05 (p-value<0.05)					
	Accuracy	1)	0.743	0.874	0.880	0.874	0.864
		2)	0.827	0.901	0.906	0.911	0.901
		3)	0.853	0.901	0.901	0.895	0.885
		4)	0.733	0.880	0.880	0.869	0.864
		5)	0.859	0.906	0.906	0.901	0.895
		6)	0.806	0.906	0.906	0.906	0.890
		GM2005: 0.525 (p-value<0.05)					
	Precision	1)	0.701	0.987	1.000	1.000	1.000
		2)	0.819	0.966	0.977	1.000	1.000
		3)	0.853	0.966	0.976	0.976	0.988
		4)	0.699	1.000	1.000	1.000	1.000
		5)	0.869	0.977	0.988	0.988	0.988
		6)	0.784	0.977	0.977	0.988	0.988
		GM2005: 0.667 (p-value<0.05)					

Table S9: Hypothesis testing results when distribution of survival time is mis-specified. Hypothesis Testing results are summarized for Simulation Setting 5. Let TPR denote true positive rate, FPR denote false positive rate, FP denote False Positive, TP denote True Positive, FN denote False Negative, and TN denote True Negative. Then $TPR = \frac{TP}{TP+FN}$, $FPR = \frac{FP}{TN+FP}$, $Accuracy = \frac{TP+TN}{TP+FP+TN+FN}$, $Precision = \frac{TP}{TP+FP}$. BF denotes Bayes Factor.

Distribution	p	Criteria	Decision Rule					
			$BF > 1$	$BF > 3$	$BF > 5$	$BF > 10$	$BF > 20$	GM2005
Weibull	5	TPR	1.000	1.000	1.000	1.000	1.000	0.970
		FPR	0.020	0.010	0.000	0.000	0.000	0.080
		Accuracy	0.990	0.995	1.000	1.000	1.000	0.945
		Precision	0.980	0.990	1.000	1.000	1.000	0.924
	50	TPR	1.000	1.000	1.000	1.000	1.000	0.360
		FPR	0.000	0.000	0.000	0.000	0.000	0.080
		Accuracy	1.000	1.000	1.000	1.000	1.000	0.640
		Precision	1.000	1.000	1.000	1.000	1.000	0.818
	100	TPR	1.000	1.000	1.000	1.000	1.000	0.320
		FPR	0.000	0.000	0.000	0.000	0.000	0.05
		Accuracy	1.000	1.000	1.000	1.000	1.000	0.635
		Precision	1.000	1.000	1.000	1.000	1.000	0.865

Table S10: Hypothesis testing results - comparisons between asymptotic procedure and permutation procedure that are proposed by Goeman et al. (2005) for $n = 30$, $g(\boldsymbol{z}_i) =$ nonparametric function.

Simulation Setting	Procedure	Criteria			
		TPR	FPR	Accuracy	Precision
Simulation Setting 2.1 ($p = 5$)	Asymptotic	0.670	0.030	0.820	0.957
	Permutation	0.670	0.030	0.820	0.957
Simulation Setting 2.2 ($p = 50$)	Asymptotic	0.190	0.070	0.560	0.731
	Permutation	0.160	0.070	0.545	0.696
Simulation Setting 2.3 ($p = 100$)	Asymptotic	0.160	0.060	0.550	0.727
	Permutation	0.140	0.070	0.535	0.667