Biostatistics (2017), **0**, 0, *pp.* 1–15
doi:10.1093/biostatistics/suppMat

Supplementary Material for "Simple fixed-effects inference for complex functional models"

SO YOUNG PARK*, ANA-MARIA STAICU, LUO XIAO

Department of Statistics, North Carolina State University, Raleigh, NC, USA

spark13@ncsu.edu

CIPRIAN M. CRAINICEANU

Department of Biostatistics, Johns Hopkins University, Baltimore, MD, USA

Section A - Section D include additional simulation results on the performance of the pointwise and joint confidence bands. Specifically, Section A presents results for different nominal coverages 85% and 90% when confidence bands are obtained by bootstrapping subject-level residuals and the mean function $\mu(t, x)$ is modeled nonparametrically. Section B presents results when confidence bands are obtained by bootstrapping subject-level residuals and the mean function $\mu(t, x)$ is modeled parametrically. Section C presents results obtained by bootstrapping observations by subject; in all sections, nominal coverages of 85%, 90% and 95% are considered. Section D presents simulation results for the case of having non-Gaussian errors. Lastly, Section E includes the additional figures referenced in the main manuscript.

Section A. Additional results obtained by bootstrapping Residuals by subject when a nonparametric bivariate function is fitted for $\mu(t, x)$

In practice one does not know the true model for the mean structure and thus nonparametric modeling is often preferable. Thus instead of assuming a correct parametric model for $\mu(t, x)$, we consider a completely nonparametric dependence of the mean response on t and X. For example, in the case of F2 i. (a) the generating mean model is $\mu(t, x) = 5 + 2t + 3X$, but the assumed fitting model is an unknown, smooth bivariate function of both t and X. The relevant results are presented in Tables S1-S2 for nominal coverages of 85% and 90%, respectively. The simulation data are generated as described in Section 6. We use the residual-based bootstrap. Both pointwise and joint confidence bands perform excellently for all three cases of true mean functions, and for all three nominal coverages we consider here.

Table S1. Simulation results for 85% confidence bands based on the bootstrap of subject-level residuals when a *nonparametric* bivariate function is fitted for $\mu(t, x)$; results are based on 500 MC samples.

Case	True Mean Function	Parameter	ρ	$\text{ACP}^{\text{point}}$		AL^{point}		$\text{ACP}^{\text{joint}}_{\mu(t,x)}$		$\text{AL}^{\text{joint}}_{\mu(t,x)}$	
(a)	$\beta_0 + \beta_t t + \beta_x X + \tau Z$	$\mu(t, X) = 5 + 2t + 3X$	0.20	0.84	(< 0.01)	1.22	(0.01)	0.82	(0.02)	2.85	(0.01)
			0.90	0.83	(< 0.01)	1.61	(0.01)	0.81	(0.02)	3.76	(0.01)
		$\tau = 8$	0.20	0.84	(0.02)	0.10	(< 0.01)				
			0.90	0.84	(0.02)	0.10	(< 0.01)				
(b)	$\beta_0 + \beta_t t + \beta_x X + \beta_{tx} tX + \tau Z$	$\mu(t, X) = 5 + 2t + 3X + 7tX$	0.20	0.84	(< 0.01)	1.22	(0.01)	0.82	(0.02)	2.85	(0.01)
			0.90	0.83	(< 0.01)	1.61	(0.01)	0.81	(0.02)	3.76	(0.01)
		$\tau = 8$	0.20	0.84	(0.02)	0.10	(< 0.01)				
			0.90	0.84	(0.02)	0.10	(< 0.01)				
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$\mu(t, X) = \cos(2\pi t) + 3X$	0.20	0.84	(< 0.01)	1.22	(0.01)	0.82	(0.02)	2.86	(0.01)
			0.90	0.83	(< 0.01)	1.61	(0.01)	0.81	(0.02)	3.77	(0.01)
		$\tau = 8$	0.20	0.84	(0.02)	0.10	(¡ 0.01)				
			0.90	0.84	(0.02)	0.10	(¡ 0.01)				

Standard errors are presented in parentheses.

Table S2. Simulation results for 90% confidence bands based on the bootstrap of subject-level residuals when a *nonparametric* bivariate function is fitted for $\mu(t, x)$; results are based on 500 MC samples.

Case	True Mean Function	Parameter	ρ	$\text{ACP}^{\text{point}}$		AL^{point}		$\text{ACP}^{\text{joint}}_{\mu(t,X)}$		$\text{AL}^{\text{joint}}_{\mu(t,X)}$	
(a)	$\beta_0 + \beta_t t + \beta_x X + \tau Z$	$\mu(t, X) = 5 + 2t + 3X$	0.20	0.89	(< 0.01)	1.39	(0.01)	0.87	(0.01)	2.99	(0.01)
			0.90	0.88	(< 0.01)	1.83	(0.02)	0.87	(0.02)	3.95	(0.01)
		$\tau = 8$	0.20	0.88	(0.01)	0.12	(< 0.01)				
			0.90	0.88	(0.01)	0.12	(< 0.01)				
(b)	$\beta_0 + \beta_t t + \beta_x X + \beta_{tx} tX + \tau Z$	$\mu(t, X) = 5 + 2t + 3X + 7tX$	0.20	0.89	(< 0.01)	1.39	(0.01)	0.87	(0.01)	2.99	(0.01)
			0.90	0.88	(< 0.01)	1.83	(0.02)	0.87	(0.02)	3.95	(0.01)
		$\tau = 8$	0.20	0.88	(0.01)	0.12	(< 0.01)				
			0.90	0.88	(0.01)	0.12	(< 0.01)				
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$\mu(t, X) = \cos(2\pi t) + 3X$	0.20	0.89	(< 0.01)	1.39	(0.01)	0.88	(0.01)	3.00	(0.01)
			0.90	0.88	(< 0.01)	1.84	(0.02)	0.87	(0.02)	3.96	(0.01)
		$\tau = 8$	0.20	0.88	(0.01)	0.12	(< 0.01)				
			0.90	0.88	(0.01)	0.12	(< 0.01)				

Standard errors are presented in parentheses.

Section B. Results obtained by bootstrapping residuals by subject when the correct mean structure is fitted

Here we present the performance of the pointwise and joint confidence bands for different nominal coverages when the correct models are assumed. Estimation accuracy is measured using the bias and variance of the estimators; for univariate and bivariate smooths, single number summaries of these measures are used. Specifically, when the mean of interest is $\mu(t) = \cos(2\pi t)$, as in scenario F2 i.(c), the integrated bias defined by $\int_0^1 \{\bar{\mu}(t) - \mu(t)\}dt$ is used as a summary measure of bias, and the integrated variance, defined by $\int_0^1 \{\sum_{i_{sim}=1}^{N_{sim}} \{\widehat{\mu}_{i_{sim}}(t) - \bar{\mu}(t)\}^2/(N_{sim} - 1)\}dt$ is used as a summary measure of variance. Here $\widehat{\mu}_{i_{sim}}(t)$ denotes the mean estimator from one simulation, $\bar{\mu}(t) = \sum_{i_{sim}=1}^{N_{sim}} \widehat{\mu}_{i_{sim}}(t)/N_{sim}$ is the sample mean of the estimator $\widehat{\mu}(t)$.

Tables S3, S4, and S5 show results for nominal coverage of 85%, 90% and 95% respectively. The pointwise confidence interval/bands for all nominal coverages perform fairly well while there are few cases where they fail to achieve their nominal coverages. For the joint confidence band, the 90% ones perform very well for all cases considered, whereas the 85% one fails to achieve the nominal coverage for some cases. In terms of average lengths, the confidence intervals/bands tend to be wider when there is stronger correlation.

Table S3. Simulation results for 85% confidence bands based on the bootstrap of subject-level residuals when the *correct* mean structure is fitted; results are based on 500 MC samples.

Case	True Mean Function	Parameter	ρ	Bias	$\sqrt{\text{var}}$	$\text{ACP}^{\text{point}}$	AL^{point}	$\text{ACP}^{\text{joint}}_{\mu(t,X)}$	$\text{AL}^{\text{joint}}_{\mu(t,X)}$
(a)	$\beta_0 + \beta_t t + \beta_x X + \tau Z$	$\beta_0 = 5$	0.20	0.00	0.20	0.83 (0.02)	0.40 ($<$ 0.01)		
			0.90	-0.01	0.27	0.84 (0.02)	0.52 ($<$ 0.01)		
		$\beta_t = 2$	0.20	0.01	0.40	0.83 (0.02)	0.78 ($<$ 0.01)		
			0.90	0.01	0.52	0.83 (0.02)	1.03 ($<$ 0.01)		
		$\beta_x = 3$	0.20	0.00	0.05	0.84 (0.02)	0.10 ($<$ 0.01)		
			0.90	0.00	0.05	0.84 (0.02)	0.10 ($<$ 0.01)		
		$\tau = 8$	0.20	0.00	0.05	0.84 (0.02)	0.10 ($<$ 0.01)		
			0.90	0.00	0.05	0.83 (0.02)	0.10 ($<$ 0.01)		
(b)	$\beta_0 + \beta_t t + \beta_x X + \beta_{tx} tX + \tau Z$	$\beta_0 = 5$	0.20	-0.01	0.39	0.84 (0.02)	0.77 ($<$ 0.01)		
			0.90	-0.02	0.51	0.84 (0.02)	1.01 ($<$ 0.01)		
		$\beta_t = 2$	0.20	0.03	0.78	0.84 (0.02)	1.54 (0.01)		
			0.90	0.04	1.02	0.84 (0.02)	2.01 (0.01)		
		$\beta_x = 3$	0.20	0.02	0.67	0.84 (0.02)	1.33 (0.01)		
			0.90	0.02	0.88	0.82 (0.02)	1.74 (0.01)		
		$\beta_{tx} = 7$	0.20	-0.04	1.33	0.83 (0.02)	2.65 (0.01)		
			0.90	-0.06	1.75	0.83 (0.02)	3.47 (0.01)		
		$\tau = 8$	0.20	0.00	0.05	0.84 (0.02)	0.10 ($<$ 0.01)		
			0.90	0.00	0.05	0.83 (0.02)	0.10 ($<$ 0.01)		
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$f(t) = \cos(2\pi t)$	0.20	0.00	0.25	0.83 (0.01)	0.49 ($<$ 0.01)	0.81 (0.02)	0.77 ($<$ 0.01)
			0.90	0.00	0.32	0.83 (0.01)	0.64 ($<$ 0.01)	0.81 (0.02)	1.00 ($<$ 0.01)
		$\beta_x = 3$	0.20	0.00	0.05	0.84 (0.02)	0.10 ($<$ 0.01)		
			0.90	0.00	0.05	0.84 (0.02)	0.10 ($<$ 0.01)		
		$\tau = 8$	0.20	0.00	0.05	0.84 (0.02)	0.10 ($<$ 0.01)		
			0.90	0.00	0.05	0.83 (0.02)	0.10 ($<$ 0.01)		
(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.00	0.61	0.84 ($<$ 0.01)	1.22 (0.01)	0.81 (0.02)	2.86 (0.01)
			0.90	0.00	0.81	0.83 ($<$ 0.01)	1.61 (0.01)	0.80 (0.02)	3.77 (0.01)
		$\tau = 8$	0.20	0.00	0.05	0.84 (0.02)	0.10 ($<$ 0.01)		
			0.90	0.00	0.05	0.84 (0.02)	0.10 ($<$ 0.01)		

Standard errors are presented in parentheses.

Table S4. Simulation results for 90% confidence bands based on the bootstrap of subject-level residuals when the *correct* mean structure is fitted; results are based on 500 MC samples.

Case	True Mean Function	Parameter	ρ	Bias	$\sqrt{\text{var}}$	$\text{ACP}^{\text{point}}$	AL^{point}	$\text{ACP}^{\text{joint}}_{\mu(t,X)}$	$\text{AL}^{\text{joint}}_{\mu(t,X)}$
(a)	$\beta_0 + \beta_t t + \beta_x X + \tau Z$	$\beta_0 = 5$	0.20	0.00	0.20	0.89 (0.01)	0.46 ($<$ 0.01)		
			0.90	-0.01	0.27	0.89 (0.01)	0.59 ($<$ 0.01)		
		$\beta_t = 2$	0.20	0.01	0.40	0.89 (0.01)	0.89 ($<$ 0.01)		
			0.90	0.01	0.52	0.89 (0.01)	1.17 ($<$ 0.01)		
		$\beta_x = 3$	0.20	0.00	0.05	0.89 (0.01)	0.11 ($<$ 0.01)		
			0.90	0.00	0.05	0.89 (0.01)	0.12 ($<$ 0.01)		
		$\tau = 8$	0.20	0.00	0.05	0.90 (0.01)	0.12 ($<$ 0.01)		
			0.90	0.00	0.05	0.89 (0.01)	0.12 ($<$ 0.01)		
(b)	$\beta_0 + \beta_t t + \beta_x X + \beta_{tx} tX + \tau Z$	$\beta_0 = 5$	0.20	-0.01	0.39	0.89 (0.01)	0.88 ($<$ 0.01)		
			0.90	-0.02	0.51	0.87 (0.01)	1.15 (0.01)		
		$\beta_t = 2$	0.20	0.03	0.78	0.89 (0.01)	1.75 (0.01)		
			0.90	0.04	1.02	0.88 (0.01)	2.30 (0.01)		
		$\beta_x = 3$	0.20	0.02	0.67	0.88 (0.01)	1.52 (0.01)		
			0.90	0.02	0.88	0.87 (0.01)	1.98 (0.01)		
		$\beta_{tx} = 7$	0.20	-0.04	1.33	0.88 (0.01)	3.03 (0.01)		
			0.90	-0.06	1.75	0.87 (0.01)	3.96 (0.02)		
		$\tau = 8$	0.20	0.00	0.05	0.9 (0.01)	0.12 ($<$ 0.01)		
			0.90	0.00	0.05	0.89 (0.01)	0.12 ($<$ 0.01)		
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$f(t) = \cos(2\pi t)$	0.20	0.00	0.25	0.88 (0.01)	0.56 ($<$ 0.01)	0.87 (0.02)	0.84 ($<$ 0.01)
			0.90	0.00	0.32	0.88 (0.01)	0.73 ($<$ 0.01)	0.87 (0.01)	1.09 ($<$ 0.01)
		$\beta_x = 3$	0.20	0.00	0.05	0.89 (0.01)	0.11 ($<$ 0.01)		
			0.90	0.00	0.05	0.89 (0.01)	0.12 ($<$ 0.01)		
		$\tau = 8$	0.20	0.00	0.05	0.90 (0.01)	0.12 ($<$ 0.01)		
			0.90	0.00	0.05	0.89 (0.01)	0.12 ($<$ 0.01)		
(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.00	0.61	0.89 ($<$ 0.01)	1.40 (0.01)	0.87 (0.01)	3.01 (0.01)
			0.90	0.00	0.81	0.88 ($<$ 0.01)	1.84 (0.02)	0.86 (0.02)	3.96 (0.01)
		$\tau = 8$	0.20	0.00	0.05	0.88 (0.01)	0.12 ($<$ 0.01)		
			0.90	0.00	0.05	0.88 (0.01)	0.12 ($<$ 0.01)		

Standard errors are presented in parentheses.

Table S5. Simulation results for 95% confidence bands based on the bootstrap of subject-level residuals when the *correct* mean structure is fitted; results are based on 500 MC samples.

Case	True Mean Function	Parameter	ρ	Bias	$\sqrt{\text{var}}$	$\text{ACP}^{\text{point}}$	AL^{point}	$\text{ACP}^{\text{joint}}_{\mu(t,X)}$	$\text{AL}^{\text{joint}}_{\mu(t,X)}$
(a)	$\beta_0 + \beta_t t + \beta_x X + \tau Z$	$\beta_0 = 5$	0.20	0.00	0.20	0.94 (0.01)	0.54 (<0.01)		
			0.90	-0.01	0.27	0.94 (0.01)	0.70 (<0.01)		
		$\beta_t = 2$	0.20	0.01	0.40	0.94 (0.01)	1.06 (<0.01)		
			0.90	0.01	0.52	0.94 (0.01)	1.39 (0.01)		
		$\beta_x = 3$	0.20	0.00	0.05	0.95 (0.01)	0.14 (<0.01)		
			0.90	0.00	0.05	0.95 (0.01)	0.14 (<0.01)		
		$\tau = 8$	0.20	0.00	0.05	0.93 (0.01)	0.14 (<0.01)		
			0.90	0.00	0.05	0.93 (0.01)	0.14 (<0.01)		
(b)	$\beta_0 + \beta_t t + \beta_x X + \beta_{tx} tX + \tau Z$	$\beta_0 = 5$	0.20	-0.01	0.39	0.93 (0.01)	1.04 (<0.01)		
			0.90	-0.02	0.51	0.94 (0.01)	1.36 (0.01)		
		$\beta_t = 2$	0.20	0.03	0.78	0.93 (0.01)	2.07 (0.01)		
			0.90	0.04	1.02	0.94 (0.01)	2.72 (0.01)		
		$\beta_x = 3$	0.20	0.02	0.67	0.93 (0.01)	1.08 (0.01)		
			0.90	0.02	0.88	0.93 (0.01)	2.36 (0.01)		
		$\beta_{tx} = 7$	0.20	-0.04	1.33	0.92 (0.01)	3.60 (0.02)		
			0.90	-0.06	1.75	0.93 (0.01)	4.71 (0.02)		
		$\tau = 8$	0.20	0.00	0.05	0.93 (0.01)	0.14 (<0.01)		
			0.90	0.00	0.05	0.93 (0.01)	0.14 (<0.01)		
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$f(t) = \cos(2\pi t)$	0.20	0.00	0.25	0.93 (0.01)	0.67 (<0.01)	0.92 (0.01)	0.95 (<0.01)
			0.90	0.00	0.32	0.93 (0.01)	0.87 (<0.01)	0.93 (0.01)	1.23 (<0.01)
		$\beta_x = 3$	0.20	0.00	0.05	0.95 (0.01)	0.14 (<0.01)		
			0.90	0.00	0.05	0.95 (0.01)	0.14 (<0.01)		
		$\tau = 8$	0.20	0.00	0.05	0.93 (0.01)	0.14 (<0.01)		
			0.90	0.00	0.05	0.93 (0.01)	0.14 (<0.01)		
(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.00	0.61	0.94 (<0.01)	1.65 (0.01)	0.93 (0.01)	3.23 (0.01)
			0.90	0.00	0.81	0.94 (<0.01)	2.18 (0.02)	0.93 (0.01)	4.26 (0.01)
		$\tau = 8$	0.20	0.00	0.05	0.93 (0.01)	0.14 (<0.01)		
			0.90	0.00	0.05	0.94 (0.01)	0.14 (<0.01)		

Standard errors are presented in parentheses.

Section C. Results obtained by bootstrapping observations by subject when the correct mean structure is fitted

Here we investigate the performance of pointwise and joint confidence interval/bands when they are obtained by bootstrapping subject-level observations (Algorithm 1) instead of bootstrapping subject-level residuals (Algorithm 2). Tables S6 - S8 present the relevant results for nominal coverages of 85%, 90% and 95% respectively.

First focus the case when the effect of covariate X is linear on the mean response (cases F2 i. (a)-(c)). Consider the setting described in Section 6 of the main manuscript, and recall that for each subject a single scalar covariate of interest X_i is observed. The simulation results confirm that bootstrapping subject-level observations instead of residuals has no effect on the performance of pointwise and joint confidence interval/bands, and overall they perform well. However, for the case of smooth effect of X, the result for the joint confidence band obtained by bootstrapping subject-level observations show substantial under-coverage. We suspect that it is because our covariate X is subject-specific, i.e. X_i is time-invariant; With $n = 100$ subjects in our MC samples, there are only 100 X_i-values to resample from. To confirm our speculation, we consider time-varying covariate (i.e. X_{ij} instead of X_i). The results are presented in Table S9, and the empirical coverages are similar to ones obtained with the residual-based bootstrap.

Table S6. Simulation results for 85% confidence bands based on the bootstrap of subject-level observations when the *correct* mean structure is fitted; results are based on 500 MC samples.

Case	True Mean Function	Parameter	ρ	Bias	$\sqrt{\text{var}}$	$\text{ACP}^{\text{point}}$	AL^{point}	$\text{ACP}^{\text{joint}}_{\mu(t,X)}$	$\text{AL}^{\text{joint}}_{\mu(t,X)}$
(a)	$\beta_0+\beta_t t+\beta_x X+\tau Z$	$\beta_0=5$	0.20	0.00	0.20	0.83 (0.02)	0.40 (< 0.01)		
			0.90	-0.01	0.27	0.84 (0.02)	0.52 (< 0.01)		
		$\beta_t=2$	0.20	0.01	0.40	0.83 (0.02)	0.78 (< 0.01)		
			0.90	0.01	0.52	0.83 (0.02)	1.03 (< 0.01)		
		$\beta_x=3$	0.20	0.00	0.05	0.85 (0.02)	0.10 (< 0.01)		
			0.90	0.00	0.05	0.84 (0.02)	0.10 (< 0.01)		
		$\tau=8$	0.20	0.00	0.05	0.83 (0.02)	0.10 (< 0.01)		
			0.90	0.00	0.05	0.83 (0.02)	0.11 (< 0.01)		
(b)	$\beta_0+\beta_t t+\beta_x X+\beta_{tx}tX+\tau Z$	$\beta_0=5$	0.20	-0.01	0.39	0.83 (0.02)	0.77 (< 0.01)		
			0.90	-0.02	0.51	0.84 (0.02)	1.01 (0.01)		
		$\beta_t=2$	0.20	0.03	0.78	0.83 (0.02)	1.54 (0.01)		
			0.90	0.04	1.02	0.84 (0.02)	2.02 (0.01)		
		$\beta_x=3$	0.20	0.02	0.67	0.84 (0.02)	1.33 (0.01)		
			0.90	0.03	0.88	0.83 (0.02)	1.75 (0.01)		
		$\beta_{tx}=7$	0.20	-0.04	1.34	0.84 (0.02)	2.66 (0.01)		
			0.90	-0.06	1.75	0.84 (0.02)	3.48 (0.02)		
		$\tau=8$	0.20	0.00	0.05	0.83 (0.02)	0.10 (< 0.01)		
			0.90	0.00	0.05	0.83 (0.02)	0.11 (< 0.01)		
(c)	$\cos(2\pi t)+\beta_x X+\tau Z$	$f(t)=\cos(2\pi t)$	0.20	0.00	0.25	0.83 (0.01)	0.49 (< 0.01)	0.81 (0.02)	0.77 (< 0.01)
			0.90	0.00	0.32	0.83 (0.01)	0.64 (< 0.01)	0.81 (0.02)	1.00 (< 0.01)
		$\beta_x=3$	0.20	0.00	0.05	0.85 (0.02)	0.10 (< 0.01)		
			0.90	0.00	0.05	0.84 (0.02)	0.10 (< 0.01)		
		$\tau=8$	0.20	0.00	0.05	0.83 (0.02)	0.10 (< 0.01)		
			0.90	0.00	0.05	0.83 (0.02)	0.11 (< 0.01)		
(d)	$\cos(2\pi t)+4((X/4)-t)^3+\tau Z$	$\mu_4(t,X)$	0.20	0.00	0.64	0.82 (< 0.01)	1.25 (0.01)	0.74 (0.02)	3.00 (0.01)
			0.90	0.00	0.84	0.82 (< 0.01)	1.65 (0.01)	0.76 (0.02)	3.96 (0.01)
		$\tau=8$	0.20	0.00	0.05	0.85 (0.02)	0.11 (< 0.01)		
			0.90	0.00	0.05	0.83 (0.02)	0.11 (< 0.01)		

Standard errors are presented in parentheses.

Table S7. Simulation results for 90% confidence bands based on the bootstrap of subject-level observations when the *correct* mean structure is fitted; results are based on 500 MC samples.

Case	True Mean Function	Parameter	ρ	Bias	$\sqrt{\text{var}}$	$\text{ACP}^{\text{point}}$	AL^{point}	$\text{ACP}^{\text{joint}}_{\mu(t,X)}$	$\text{AL}^{\text{joint}}_{\mu(t,X)}$
(a)	$\beta_0+\beta_t t+\beta_x X+\tau Z$	$\beta_0=5$	0.20	0.00	0.20	0.88 (0.01)	0.46 (< 0.01)		
			0.90	-0.01	0.27	0.88 (0.01)	0.59 (< 0.01)		
		$\beta_t=2$	0.20	0.01	0.40	0.89 (0.01)	0.89 (< 0.01)		
			0.90	0.01	0.52	0.89 (0.01)	1.17 (< 0.01)		
		$\beta_x=3$	0.20	0.00	0.05	0.88 (0.01)	0.12 (< 0.01)		
			0.90	0.00	0.05	0.89 (0.01)	0.12 (< 0.01)		
		$\tau=8$	0.20	0.00	0.05	0.88 (0.01)	0.12 (< 0.01)		
			0.90	0.00	0.05	0.88 (0.01)	0.12 (< 0.01)		
(b)	$\beta_0+\beta_t t+\beta_x X+\beta_{tx}tX+\tau Z$	$\beta_0=5$	0.20	-0.01	0.39	0.88 (0.01)	0.88 (0.01)		
			0.90	-0.02	0.51	0.87 (0.01)	1.16 (0.01)		
		$\beta_t=2$	0.20	0.03	0.78	0.88 (0.01)	1.75 (0.01)		
			0.90	0.04	1.02	0.89 (0.01)	2.30 (0.01)		
		$\beta_x=3$	0.20	0.02	0.67	0.88 (0.01)	1.52 (0.01)		
			0.90	0.03	0.88	0.88 (0.01)	1.99 (0.01)		
		$\beta_{tx}=7$	0.20	-0.04	1.34	0.88 (0.01)	3.03 (0.02)		
			0.90	-0.06	1.75	0.88 (0.01)	3.97 (0.02)		
		$\tau=8$	0.20	0.00	0.05	0.88 (0.01)	0.12 (< 0.01)		
			0.90	0.00	0.05	0.88 (0.01)	0.12 (< 0.01)		
(c)	$\cos(2\pi t)+\beta_x X+\tau Z$	$f(t)=\cos(2\pi t)$	0.20	0.00	0.25	0.88 (0.01)	0.56 (< 0.01)	0.87 (0.02)	0.84 (< 0.01)
			0.90	0.00	0.32	0.88 (0.01)	0.73 (< 0.01)	0.87 (0.01)	1.09 (< 0.01)
		$\beta_x=3$	0.20	0.00	0.05	0.88 (0.01)	0.12 (< 0.01)		
			0.90	0.00	0.05	0.89 (0.01)	0.12 (< 0.01)		
		$\tau=8$	0.20	0.00	0.05	0.88 (0.01)	0.12 (< 0.01)		
			0.90	0.00	0.05	0.88 (0.01)	0.12 (< 0.01)		
(d)	$\cos(2\pi t)+4((X/4)-t)^3+\tau Z$	$\mu_4(t,X)$	0.20	0.00	0.64	0.87 (< 0.01)	1.44 (0.01)	0.81 (0.02)	3.16 (0.01)
			0.90	0.00	0.84	0.87 (< 0.01)	1.89 (0.02)	0.81 (0.02)	4.17 (0.01)
		$\tau=8$	0.20	0.00	0.05	0.89 (0.01)	0.12 (< 0.01)		
			0.90	0.00	0.05	0.88 (0.01)	0.12 (< 0.01)		

Standard errors are presented in parentheses.

Table S8. Simulation results for 95% confidence bands based on the bootstrap of subject-level observations when the *correct* mean structure is fitted; results are based on 500 MC samples.

Case	True Mean Function	Parameter	ρ	Bias	$\sqrt{\text{var}}$	$\text{ACP}^{\text{point}}$		AL^{point}		$\text{ACP}^{\text{joint}}_{\mu(t,X)}$		$\text{AL}^{\text{joint}}_{\mu(t,X)}$	
(a)	$\beta_0 + \beta_t t + \beta_x X + \tau Z$	$\beta_0 = 5$	0.20	0.00	0.20	0.94	(0.01)	0.54	(< 0.01)				
			0.90	-0.01	0.27	0.94	(0.01)	0.70	(< 0.01)				
		$\beta_t = 2$	0.20	0.01	0.40	0.94	(0.01)	1.06	(< 0.01)				
			0.90	0.01	0.52	0.94	(0.01)	1.39	(0.01)				
		$\beta_x = 3$	0.20	0.00	0.05	0.95	(0.01)	0.14	(< 0.01)				
			0.90	0.00	0.05	0.94	(0.01)	0.14	(< 0.01)				
		$\tau = 8$	0.20	0.00	0.05	0.92	(0.01)	0.14	(< 0.01)				
			0.90	0.00	0.05	0.93	(0.01)	0.14	(< 0.01)				
(b)	$\beta_0 + \beta_t t + \beta_x X + \beta_{tx} tX + \tau Z$	$\beta_0 = 5$	0.20	-0.01	0.39	0.93	(0.01)	1.05	(0.01)				
			0.90	-0.02	0.51	0.92	(0.01)	1.38	(0.01)				
		$\beta_t = 2$	0.20	0.03	0.78	0.93	(0.01)	2.09	(0.01)				
			0.90	0.04	1.02	0.93	(0.01)	2.74	(0.02)				
		$\beta_x = 3$	0.20	0.02	0.67	0.92	(0.01)	1.81	(0.01)				
			0.90	0.03	0.88	0.93	(0.01)	2.36	(0.01)				
		$\beta_{tx} = 7$	0.20	-0.04	1.34	0.93	(0.01)	3.60	(0.02)				
			0.90	-0.06	1.75	0.94	(0.01)	4.72	(0.02)				
		$\tau = 8$	0.20	0.00	0.05	0.92	(0.01)	0.14	(< 0.01)				
			0.90	0.00	0.05	0.93	(0.01)	0.14	(< 0.01)				
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$f(t) = \cos(2\pi t)$	0.20	0.00	0.25	0.93	(0.01)	0.67	(< 0.01)	0.92	(0.01)	0.95	(< 0.01)
			0.90	0.00	0.32	0.93	(0.01)	0.87	(< 0.01)	0.93	(0.01)	1.23	(< 0.01)
		$\beta_x = 3$	0.20	0.00	0.05	0.95	(0.01)	0.14	(< 0.01)				
			0.90	0.00	0.05	0.94	(0.01)	0.14	(< 0.01)				
		$\tau = 8$	0.20	0.00	0.05	0.92	(0.01)	0.14	(< 0.01)				
			0.90	0.00	0.05	0.93	(0.01)	0.14	(< 0.01)				
(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.00	0.64	0.93	(< 0.01)	1.72	(0.02)	0.89	(0.01)	3.41	(0.01)
			0.90	0.00	0.84	0.93	(< 0.01)	2.26	(0.02)	0.89	(0.01)	3.41	(0.01)
		$\tau = 8$	0.20	0.00	0.05	0.95	(0.01)	0.15	(< 0.01)				
			0.90	0.00	0.05	0.93	(0.01)	0.14	(< 0.01)				

Standard errors are presented in parentheses.

Table S9. Simulation results for confidence bands with different nominal coverages based on the bootstrap of subject-level observations when the *correct* mean structure is fitted and when the covariate is time-varying, i.e. X_{ij}; results are based on 500 MC samples.

Nominal Coverage	Case	True Mean Function	Parameter	ρ	$\text{ACP}^{\text{joint}}_{\mu(t,X)}$		$\text{AL}^{\text{joint}}_{\mu(t,X)}$	
85%	(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.82	(0.02)	1.96	(<0.01)
				0.90	0.80	(0.02)	2.13	(<0.01)
90%				0.20	0.86	(0.02)	2.07	(<0.01)
				0.90	0.87	(0.02)	2.25	(0.01)
95%				0.20	0.93	(0.02)	2.23	(<0.01)
				0.90	0.93	(0.01)	2.42	(0.01)

Standard errors are presented in parentheses.

Section D. Results for the case of having non-normal errors

We conduct additional simulation study to assess robustness of the proposed inferential methods to non-Gaussianity. Recall that $w_{ij}(t)$ is white noises in the error term, $\epsilon_{ij}(t) = \sum_{l=1}^{3} \xi_{ijl}\phi_l(t) + w_{ij}(t)$, defined in Section 6. Here we consider two non-Gaussian distributions to generate $w_{ij}(t)$: namely, (1) t-distribution with degrees of freedom, $df \approx 2.46$, and (2) skew normal distribution with mean zero, variance $\sigma^2 = 5.33$, and skewness parameter $\zeta = 50$ (?). Skew normal random variables were generated using the `fGarch` package (?) in `R` (?). True values of the parameters, df and σ^2, are determined such that signal to noise remains to be 1. Nomal, skew normal, and t distributions used to generate white noises are shown in S5. The results are similar to the Gaussian case and suggest that the proposed methods are robust to non-Gaussian error distribution.

Table S10. Simulation results for 85% confidence bands based on the bootstrap of subject-level residuals when the *correct* mean structure is fitted and when errors are *non-Gaussian*; results are based on 500 MC samples.

					t-distribution						
Case	True Mean Function	Parameter	ρ	$\text{ACP}^{\text{point}}$		AL^{point}		$\text{ACP}^{\text{joint}}_{\mu(t,X)}$		$\text{AL}^{\text{joint}}_{\mu(t,X)}$	
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$f(t) = \cos(2\pi t)$	0.20	0.82	(0.01)	0.49	(<0.01)	0.81	(0.02)	0.77	(<0.01)
			0.90	0.82	(0.01)	0.64	(<0.01)	0.81	(0.02)	1.00	(<0.01)
		$\beta_x = 3$	0.20	0.83	(0.02)	0.10	(<0.01)				
			0.90	0.83	(0.02)	0.10	(<0.01)				
		$\tau = 8$	0.20	0.85	(0.02)	0.10	(<0.01)				
			0.90	0.85	(0.02)	0.10	(<0.01)				
(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.83	(<0.01)	1.22	(<0.01)	0.90	(0.01)	3.10	(0.01)
			0.90	0.83	(<0.01)	1.61	(<0.01)	0.88	(0.01)	4.10	(0.01)
		$\tau = 8$	0.20	0.83	(0.08)	0.10	(<0.01)				
			0.90	0.83	(0.08)	0.10	(<0.01)				
					skew-normal distribution						
Case	True Mean Function	Parameter	ρ	$\text{ACP}^{\text{point}}$		AL^{point}		$\text{ACP}^{\text{joint}}$		AL^{joint}	
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$f(t) = \cos(2\pi t)$	0.20	0.84	(0.01)	0.49	(<0.01)	0.83	(0.02)	0.77	(<0.01)
			0.90	0.84	(0.01)	0.64	(<0.01)	0.83	(0.02)	1.00	(<0.01)
		$\beta_x = 3$	0.20	0.83	(0.02)	0.10	(<0.01)				
			0.90	0.84	(0.02)	0.10	(<0.01)				
		$\tau = 8$	0.20	0.86	(0.02)	0.10	(<0.01)				
			0.90	0.85	(0.02)	0.10	(<0.01)				
(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.83	(<0.01)	1.23	(<0.01)	0.89	(0.01)	3.11	(0.01)
			0.90	0.83	(<0.01)	1.61	(<0.01)	0.89	(0.01)	4.09	(0.01)
		$\tau = 8$	0.20	0.84	(0.08)	0.10	(<0.01)				
			0.90	0.85	(0.08)	0.10	(<0.01)				

Standard errors are presented in parentheses.

Table S11. Simulation results for 90% confidence bands based on the bootstrap of subject-level residuals when the *correct* mean structure is fitted and when errors are *non-Gaussian*; results are based on 500 MC samples.

Case	True Mean Function	Parameter	ρ	$\text{ACP}^{\text{point}}$	AL^{point}	$\text{ACP}^{\text{joint}}_{\mu(t,X)}$	$\text{AL}^{\text{joint}}_{\mu(t,X)}$
		t-distribution					
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$f(t) = \cos(2\pi t)$	0.20	0.87 (0.01)	0.55 (<0.01)	0.87 (0.01)	0.84 (<0.01)
			0.90	0.87 (0.01)	0.73 (<0.01)	0.87 (0.02)	1.09 (<0.01)
		$\beta_x = 3$	0.20	0.89 (0.01)	0.11 (<0.01)		
			0.90	0.88 (0.01)	0.11 (<0.01)		
		$\tau = 8$	0.20	0.90 (0.01)	0.11 (<0.01)		
			0.90	0.89 (0.01)	0.12 (<0.01)		
(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.88 (<0.01)	1.40 (<0.01)	0.93 (0.01)	3.23 (0.01)
			0.90	0.88 (<0.01)	1.84 (<0.01)	0.92 (0.01)	4.27 (0.01)
		$\tau = 8$	0.20	0.90 (0.06)	0.11 (<0.01)		
			0.90	0.90 (0.06)	0.11 (<0.01)		
		skew-normal distribution					
Case	True Mean Function	Parameter	ρ	$\text{ACP}^{\text{point}}$	AL^{point}	$\text{ACP}^{\text{joint}}_{\mu(t,X)}$	$\text{AL}^{\text{joint}}_{\mu(t,X)}$
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$f(t) = \cos(2\pi t)$	0.20	0.89 (0.01)	0.56 (<0.01)	0.88 (0.01)	0.84 (<0.01)
			0.90	0.88 (0.01)	0.73 (<0.01)	0.87 (0.01)	1.09 (<0.01)
		$\beta_x = 3$	0.20	0.89 (0.01)	0.12 (<0.01)		
			0.90	0.89 (0.01)	0.12 (<0.01)		
		$\tau = 8$	0.20	0.90 (0.01)	0.12 (<0.01)		
			0.90	0.91 (0.01)	0.12 (<0.01)		
(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.88 (<0.01)	1.40 (<0.01)	0.92 (0.01)	3.24 (0.01)
			0.90	0.88 (<0.01)	1.84 (<0.01)	0.91 (0.01)	4.26 (0.01)
		$\tau = 8$	0.20	0.89 (0.07)	0.12 (<0.01)		
			0.90	0.89 (0.07)	0.12 (<0.01)		

Standard errors are presented in parentheses.

Table S12. Simulation results for 95% confidence bands based on the bootstrap of subject-level residuals when the *correct* mean structure is fitted and when errors are *non-Gaussian*; results are based on 500 MC samples.

Case	True Mean Function	Parameter	ρ	$\text{ACP}^{\text{point}}$	AL^{point}	$\text{ACP}^{\text{joint}}_{\mu(t,X)}$	$\text{AL}^{\text{joint}}_{\mu(t,X)}$
		t-distribution					
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$f(t) = \cos(2\pi t)$	0.20	0.93 (0.01)	0.66 (<0.01)	0.93 (0.01)	0.94 (<0.01)
			0.90	0.93 (0.01)	0.86 (<0.01)	0.93 (0.01)	1.22 (<0.01)
		$\beta_x = 3$	0.20	0.94 (0.01)	0.13 (<0.01)		
			0.90	0.94 (0.01)	0.13 (<0.01)		
		$\tau = 8$	0.20	0.94 (0.01)	0.14 (<0.01)		
			0.90	0.94 (0.01)	0.14 (<0.01)		
(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.94 (<0.01)	1.66 (<0.01)	0.96 (0.01)	3.44 (0.01)
			0.90	0.93 (<0.01)	2.18 (<0.01)	0.96 (0.01)	4.53 (0.01)
		$\tau = 8$	0.20	0.93 (0.05)	0.13 (<0.01)		
			0.90	0.93 (0.05)	0.14 (<0.01)		
		skew-normal distribution					
Case	True Mean Function	Parameter	ρ	$\text{ACP}^{\text{point}}$	AL^{point}	$\text{ACP}^{\text{joint}}$	AL^{joint}
(c)	$\cos(2\pi t) + \beta_x X + \tau Z$	$f(t) = \cos(2\pi t)$	0.20	0.94 (0.01)	0.66 (<0.01)	0.93 (0.01)	0.95 (<0.01)
			0.90	0.94 (0.01)	0.86 (<0.01)	0.94 (0.01)	1.23 (<0.01)
		$\beta_x = 3$	0.20	0.94 (0.01)	0.14 (<0.01)		
			0.90	0.94 (0.01)	0.14 (<0.01)		
		$\tau = 8$	0.20	0.95 (0.01)	0.14 (<0.01)		
			0.90	0.95 (0.01)	0.14 (<0.01)		
(d)	$\cos(2\pi t) + 4((X/4) - t)^3 + \tau Z$	$\mu_4(t, X)$	0.20	0.93 (<0.01)	1.66 (<0.01)	0.96 (0.01)	3.44 (0.01)
			0.90	0.93 (<0.01)	2.18 (0.01)	0.94 (0.01)	4.53 (0.01)
		$\tau = 8$	0.20	0.94 (0.05)	0.14 (<0.01)		
			0.90	0.94 (0.05)	0.14 (<0.01)		

Standard errors are presented in parentheses.

Table S13. Empirical Type I error of the test statistic T based on the $N_{sim} = 1000$ MC samples for the case of having non-Gaussian errors.

t-distribution							
		$\mu(t,x) = \cos(2\pi t)$, $\tau = 8$					
		$\alpha = 0.05$		$\alpha = 0.10$		$\alpha = 0.15$	
$n = 100$	$\rho = 0.2$	0.08	(0.01)	0.15	(0.01)	0.21	(0.01)
$n = 200$	$\rho = 0.2$	0.07	(0.01)	0.13	(0.01)	0.19	(0.01)
$n = 300$	$\rho = 0.2$	0.07	(0.01)	0.12	(0.01)	0.17	(0.01)
skew normal distribution							
		$\mu(t,x) = \cos(2\pi t)$, $\tau = 8$					
		$\alpha = 0.05$		$\alpha = 0.10$		$\alpha = 0.15$	
$n = 100$	$\rho = 0.2$	0.09	(0.01)	0.15	(0.01)	0.22	(0.01)
$n = 200$	$\rho = 0.2$	0.05	(0.01)	0.09	(0.01)	0.14	(0.01)
$n = 300$	$\rho = 0.2$	0.06	(0.01)	0.11	(0.01)	0.16	(0.01)

Standard errors are presented in parentheses.

SECTION E. ADDITIONAL FIGURES

Additional figures discussed in the main paper are presented in this section.

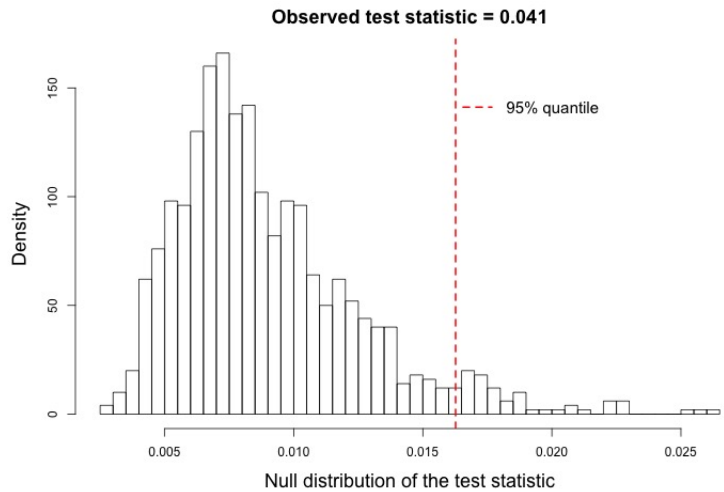

Figure S1. The null distribution of the test statistic in (4.4) for the null hypothesis that there is no effect of age on activity. The red dashed line is the 95 percent quantile of the null distribution of the test statistic.

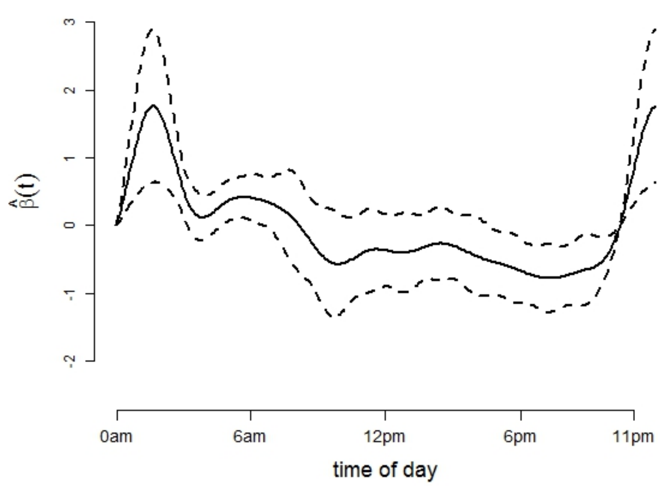

Figure S2. Association of body mass index with mean log counts as a function of time of day and the associated joint confidence bands.

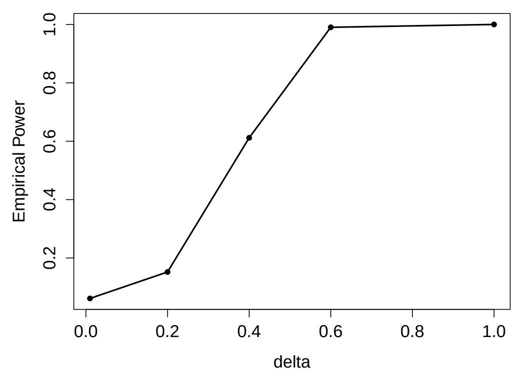

Figure S3. Estimated power curves for testing $H_0 : \mu(t, x) = \eta(t)$ using $\alpha = 0.05$, when the true mean function $\mu(t, x) = \cos(2\pi t) + \delta(\widehat{\mu}(t, x) - \cos(2\pi t))$ for $\delta = 0.01, 2, 4, 6, 8$. Results are based on $N_{sim} = 500$ MC samples.

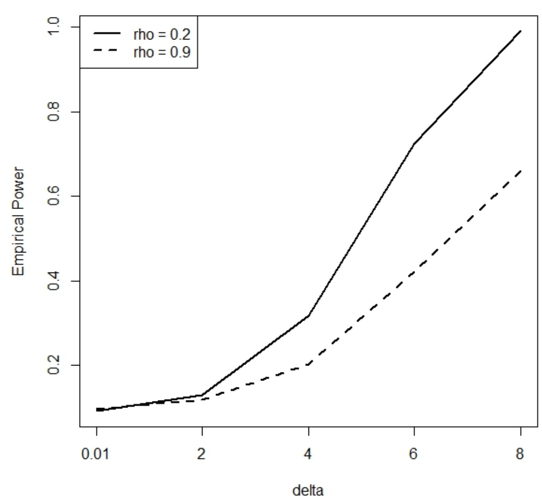

Figure S4. Estimated power curves for testing $H_0 : \mu(t, x) = \eta(t)$ using level of significance $\alpha = 0.05$, when the true mean function $\mu(t, x) = 2\cos(2\pi t) + \delta(x/4 - t)^3$ for $\delta = 0.01, 2, 4, 6$. The results are based on $N_{sim} = 500$ MC samples.

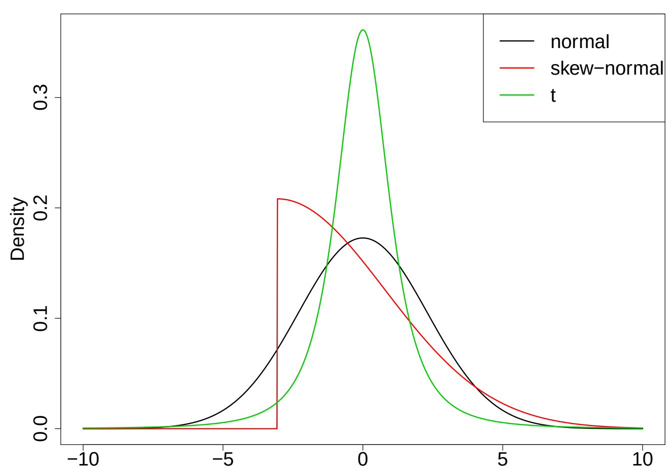

Figure S5. Normal, skew-normal, and t distributions used to generate white noises.

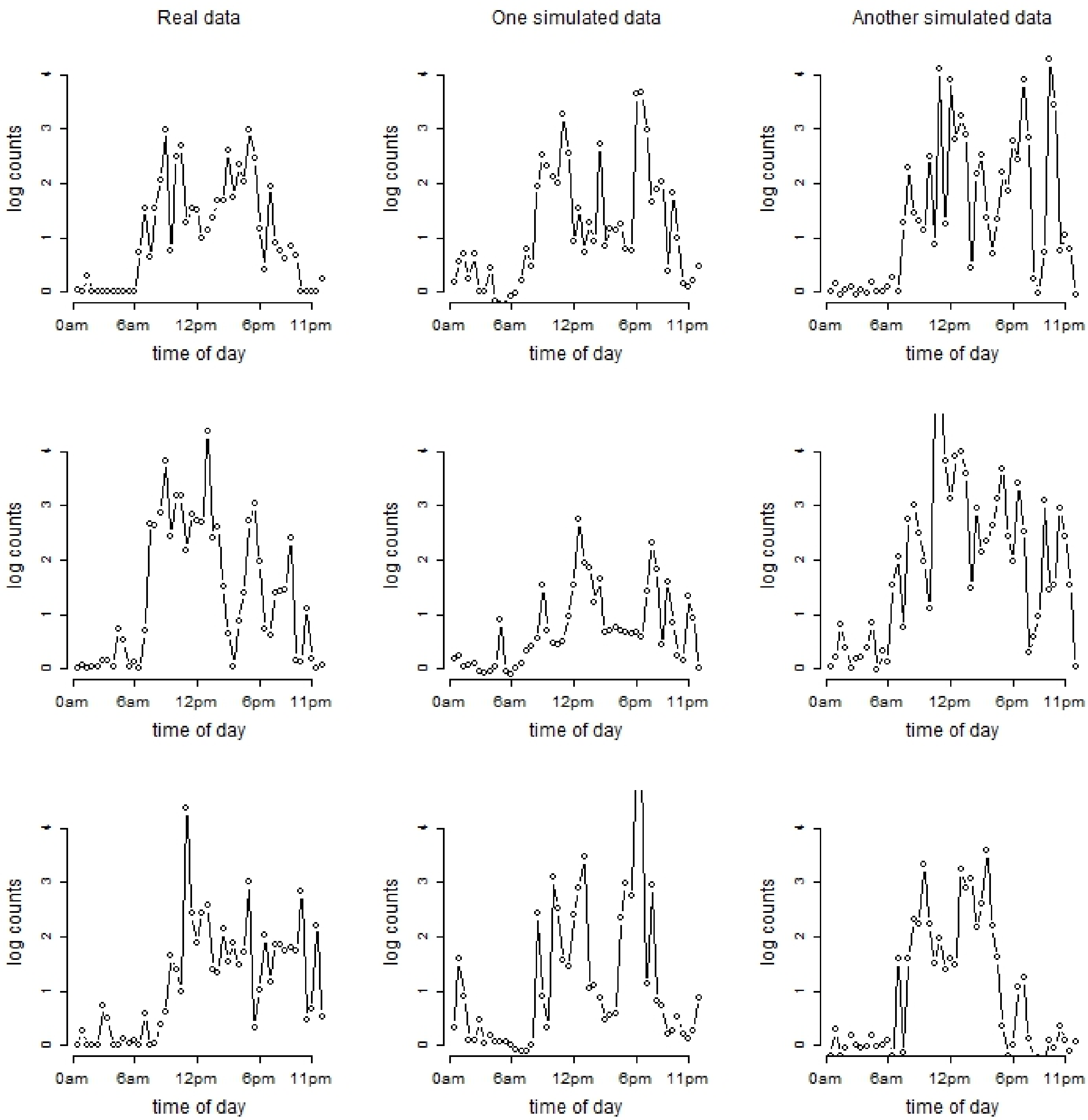

Figure S6. Three observed curves (left) from the BLSA data and the two corresponding simulated curves (middle & right) from the fitted model using the tensor product of $d_t = 15$ and $d_x = 7$ basis functions in t and x directions respectively.