Joint Modeling of Time Series Measures and Recurrent Events and Analysis of the Effects of Air Quality on Respiratory Symptoms

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Background

Significance

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- Major components of the pollutant mix of health concern are suspended particulates and ozone.
  - Suspended particles are of varying size and chemical composition. Of particular health interest are particles of mass ≤ 10 microns in diameter (PM_{10}), particles of mass ≤ 2.5 microns in diameter ($PM_{2.5}$), and sulfate (SO_4^{2-}).

Existing Studies of Air Quality

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- Zhang et al. (2000) and Gent et al. (2003)

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Yale Mothers and Infants Health (YMIH) Study
PI: Brian Leaderer, Ph.D.

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- Symptoms recorded daily include runny or stuffy nose.
- A general hypothesis is that symptom prevalence is related to air quality as well as to non-specific personal characteristics.

Variables in Our Analysis

Air quality measures include the highest daily temperature (MTMP), humidity (MHUM), COARSE (the difference between PM_{10} and $PM_{2.5}$), and SO_4^{2-} (SO4).

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- General Information
- Variables in Our Analysis
- Sample Data
- Data Summary

Literature

Model

Estimation

Simulation Study

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Sample Data

DAY	SYMP	MTMP	MHUM	COARSE	SO4	ALL	PETS	CHDC	MS
1	0	86	97	10.30	130.24	1	1	0	1
2	0	88	100	8.00	35.99	1	1	0	1
3	1	69	100	5.94	23.42	1	1	0	1
4	1	72	75	4.74	46.42	1	1	0	1
5	1	80	77	6.98	38.65	1	1	0	1
6	1	80	76	4.81	35.48	1	1	0	1
7	1	81	93	7.87	69.11	1	1	0	1
8	1	80	100	6.66	100.37	1	1	0	1
9	1	81	96	2.85	91.74	1	1	0	1
10	1	78	90	3.82	104.12	1	1	0	1
⋮	⋮		⋮	⋮		⋮	⋮	⋮	⋮
80	0	87	93	8.12	66.01	1	1	0	1
81	1	90	97	7.49	181.98	1	1	0	1
82	0	91	93	10.78	208.98	1	1	0	1
83	1	92	93	7.41	208.44	1	1	0	1

Data Summary

Variable Label	Description	Range	Summary
MTMP	Maximum 24-hour temperature	$69\text{-}100^{\mathrm{o}}$F	85.8 ± 6.9
MHUM	Maximum 24-hour Humidity	$79\text{-}100$	92.3 ± 5.6
COARSE	Coarse mode particles (PM_{10}-$PM_{2.5}$)	1.41-19.79μg/m^3	7.5 ± 3.3
SO4	24-hour sample sulfate level	6.34-306.89nm/m^3	98.3 ± 66.4
ALLERGY	Allergies diagnosed or treated by a doctor	0,1	42%(1.3%)
PETS	Fur-bearing pets kept in the home within the past year	0, 1	46%(1.3%)
CHDC	Number of children in day care(index child excluded)	0-5	45%*(1.3%)
MS	Mother's marital status	0,1	83%(4%)

* for CHDC > 0.

Literature

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- Zhang et al. (2000) introduced a simple model that uses a binary time series for each individual as the response variable against a battery of covariates.

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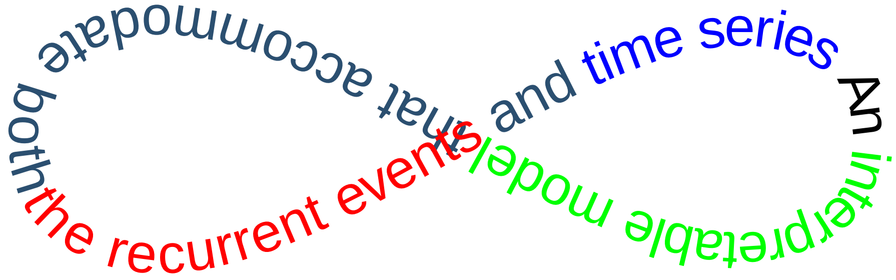

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- Limitations of Existing Models
- Zhang et al. (2000) Model
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Excellent review: Tsiatis and Davidian (2004)

Henderson, Diggle and Dobson (2000): a latent bivariate Gaussian process affects both a repeated measurement sequence and the hazard for an associated event-time.

Model

Decomposition of Time Series

$$Y_k(t) = \mu_k(t) + W_k(t) \tag{1}$$

where $W(t) = \{W_1(t), \ldots, W_m(t)\}$ is a multivariate zero-mean Gaussian process. Thus, $W_k(t)$ is specific to $Y_k(t)$.

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$$W_k(t) = q_k Q(t) + \sigma_k \mathcal{E}_k(t) \tag{2}$$

where $Q(t)$ and $\mathcal{E}(t) = \{\mathcal{E}_1(t), ..., \mathcal{E}_m(t)\}$ are independent Gaussian processes with mean zero and unit variance, and $q_k(\geq 0)$ and $\sigma_k(\geq 0)$ are coefficient parameters.

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All of the independence conditions are imposed to ensure the uniqueness of the decomposition.

Two Types of Event Transition

$\Uparrow$ Transition from a normal state ($Z = 0$) to an abnormal state ($Z = 1$), denoted by $0 \rightarrow 1$. We assume that the event intensity (hazard rate) for this transition is $\lambda_1(t)$.

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$\Downarrow$ The reverse $1 \rightarrow 0$, with event intensity $\lambda_2(t)$.

Proportional Hazards

For any individual i,

$$\lambda_{is}(t) = \exp\{X_i(t)^T \beta_s + \mathcal{B}_{is}(t)\}\lambda_s, \tag{3}$$

where

$$\mathcal{B}_{is}(t) = \gamma_{0s} U_i + \gamma_s Q(t), \tag{4}$$

and $\{U_i\}_{i=1}^n$ are subject-specific frailties which follow the standard normal distribution and are independent of $Q(t)$ and $\mathcal{E}(t)$.

Correlation

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Many different correlation structures have been proposed in the geostatistical literature (see, for example, Matérn, 1960, p.16; Cressie, 1993, pp. 85-86; Chilès and Delfiner, 1999, Section 2.5).

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We use the powered exponential correlation function:

$$\rho(\alpha, u) = \exp(-\alpha|u|^{\delta}) : 0 < \delta \leq 2. \tag{5}$$

Covariance-Stationarity

Let
$V_1 = \big(\rho_1(\alpha_1, |i-j|)\big)_{d\times d}$, where $\rho_1(\alpha_1, u)$ is defined by (5).

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$\diamond$ $\mathcal{E}_k = (\mathcal{E}_k(1), \cdots, \mathcal{E}_k(d))^T \overset{d}{\sim} N(0, V_{2k})$.

Time Series

Let

$$\begin{cases} Y &= (Y_1(1), \cdots, Y_1(d), \cdots, Y_m(1), \cdots, Y_m(d))^T, \\ \mu &= (\mu_1(1), \cdots, \mu_1(d), \cdots, \mu_m(1), \cdots, \mu_m(d))^T. \end{cases}$$

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$Y \overset{d}{\sim} N(\mu, V)$ with

$$V = \begin{pmatrix} q_1^2 V_1 + \sigma_{21}^2 V_{21} & q_1 q_2 V_1 & \cdots & q_1 q_m V_1 \\ q_2 q_1 V_1 & q_2^2 V_1 + \sigma_{22}^2 V_{22} & \cdots & q_2 q_m V_1 \\ \cdots & \cdots & \cdots & \cdots \\ q_m q_1 V_1 & q_m q_2 V_1 & \cdots & q_m^2 V_1 + \sigma_{2m}^2 V_{2m} \end{pmatrix}_{q \times q},$$

where $q = d \times m$.

Counting Processes

$$\begin{cases} N_i^{(1)}(t) = \#\{0 < u \leq t : \ Z_i(u) = 1, \ Z_i(u-) = 0\}, \\ N_i^{(1)}(0) = 0, \end{cases}$$

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Intensities

It follows from (3) that $E\left[dN_i^{(s)}(t) \,|\, Q(t), U_i\right] = \lambda_{is}(t)\,dt$ is given by the model

$$\lambda_{is}(t)\,dt = \exp\{X_i(t)^T\beta_s + \mathcal{B}_{is}(t)\}\lambda_s\,dt, \tag{6}$$

$s = 1, 2$ and $1 \leq i \leq n$.

Stopping Times

$$\begin{aligned}
\tau_{ij}^{(1)} &= \inf\{0 \le t \le T : N_i^{(1)}(t) = j\} \text{ for } 1 \le j \le N_i^{(1)}, \\
\tau_{ij}^{(2)} &= \inf\{0 \le t \le T : N_i^{(2)}(t) = j\} \text{ for } 1 \le j \le N_i^{(2)}.
\end{aligned}$$

- $N_i^{(1)} = N_i^{(2)} + 1$.
  - $0 = \tau_{i0}^{(2)} \le \tau_{i1}^{(1)} \le \tau_{i1}^{(2)} \le \cdots \le \tau_{iN_i^{(2)}}^{(1)} \le \tau_{iN_i^{(2)}}^{(2)} \le \tau_{iN_i^{(1)}}^{(1)} \le T$
- $N_i^{(2)} = N_i^{(1)}$.
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Partitioning of the Time Interval

$$C_{i1} \triangleq \begin{cases} \bigcup_{j=1}^{N_i^{(1)}} (\tau^{(2)}_{i(j-1)}, \tau^{(1)}_{ij}] \bigcup \{0\} \bigcup (\tau^{(2)}_{iN_i^{(1)}}, T] & \text{if } N_i^{(1)} = N_i^{(2)}, \\ \bigcup_{j=1}^{N_i^{(1)}} (\tau^{(2)}_{i(j-1)}, \tau^{(1)}_{ij}] \bigcup \{0\} & \text{if } N_i^{(1)} = N_i^{(2)} + 1, \end{cases}$$

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$N_i^{(1)}$ and $N_i^{(2)}$ jump on C_{i1} and C_{i2}, respectively.

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- $N = \{(N_i^{(1)}(t),\, N_i^{(2)}(t)) :\, 0 < t \leq T\}_{i=1}^n$

Likelihood Function

$$L(\theta) = L_1(\theta, Y) E_{(Q,U)|Y}\left[L_2(\theta, N \mid Q, U)\right], \qquad (7)$$

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Conditional Likelihood

$$
\begin{aligned}
& L_2(\theta, N \,|\, Q, U) \\
= & \left(\prod_{i=1}^{n} \prod_{s=1}^{2} \prod_{t \in C_{is}} \lambda_{is}(t)^{\Delta N_i^{(s)}(t)} \right) \times \\
& \exp\left[- \sum_{i=1}^{n} \sum_{s=1}^{2} \int_0^T \lambda_{is}(t) I(u \in C_{is})\, du \right] \\
= & \left(\prod_{i=1}^{n} \prod_{s=1}^{2} \prod_{t \in C_{is}} \left[\exp\{X_i^T(t)\beta_s + \mathcal{B}_{is}(t)\}\lambda_s \right]^{\Delta N_i^{(s)}(t)} \right) \times \\
& \exp\left[- \sum_{i=1}^{n} \sum_{s=1}^{2} \int_0^T \exp\{X_i^T(u)\beta_s + \mathcal{B}_{is}(u)\}\lambda_s I(u \in C_{is})\, du \right],
\end{aligned}
$$

where $I(\cdot)$ is an indicator function, and $\Delta N_i^{(s)}(t) = N_i^{(s)}(t) - N_i^{(s)}(t-)$.

Estimation

Two-stage Procedure

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2. Treat the maximum likelihood estimates from Stage 1 as if they are known and use the counting processes model (6) to estimate parameters $\beta_s, \gamma_{0s}, \gamma_s, \lambda_s \ (s = 1, 2)$ by maximizing the likelihood function $E_{(Q,U)|Y}\left[L_2(\theta, N \mid Q, U)\right]$.

Stage 1

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To reduce computational complexity, we can pre-estimate μ by a weighted moving average,

$$\widehat{\mu}_k(t) = \sum_{s=-m_0}^{m_0} w(s) Y_k(t+s) \tag{8}$$

for pre-specified non-zero weights $\{w(s):\ s = -m_0, -m_0+1, \cdots, 0, \cdots, m_0-1, m_0\}$.

Stage 2

We use the EM algorithm (Dempster, Laird and Rubin, 1977) to maximize

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In the maximization step, we use a Newton-Raphson algorithm to maximize $E_{\theta^{(0)}}[l_2(\theta, N, Q, U)|N]$ and obtain an updated point estimate for θ.

Simulation Study

Stage 1: Time Series Model

- Using model (2) and assuming $\sigma_k = q_k$, we generated a two dimensional time series Y, i.e., $\{Y(t) = (Y_1(t), Y_2(t))^T\}_{t=1}^d$ for d days, where d was chosen to be either 30 or 50.

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- Each simulation was replicated 1000 times.

Effect of Correlation Parameter $\delta = .5$

Parameter	True Value	d=30		d=50	
		Estimate	S.E.	Estimate	S.E.
α	.81	1.375	1.732	1.081	0.622
q_1	1.0	0.916	0.130	0.935	0.102
q_2	1.0	0.908	0.131	0.940	0.104

Effect of Correlation Parameter $\delta = 2$

Parameter	True Value	d=30		d=50	
		Estimate	S.E.	Estimate	S.E.
α	0.81	0.971	0.334	0.897	0.208
q_1	1.0	0.962	0.138	0.975	0.099
q_2	1.0	0.956	0.132	0.975	0.104

Effect of Nonstationarity

We used the following model to simulate a non-stationary process

$$Y_k(t) = \mu_k(t) + q_k Q(t) + \sigma(t)\mathcal{E}_k(t), \tag{9}$$

where $Q(t)$ and $\mathcal{E}_k(t)$ are independent stationary Gaussian processes, whilst the function $\sigma(t)$ was generated from the χ^2_1 distribution at the discrete time points to introduce the nonstationarity for $Y_k(t)$.

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where $Q(t)$ and $\mathcal{E}_k(t)$ are independent stationary Gaussian processes, whilst the function $\sigma(t)$ was generated from the χ_1^2 distribution at the discrete time points to introduce the nonstationarity for $Y_k(t)$.

When $d = 30$, in roughly 10% of the simulations our estimation procedure failed to converge. When $d = 50$, the estimation procedure failed to converge in about 4% of the simulations. This computational problem is due to the difficulty of estimating α under the stationary assumption.

Parameter Estimates under Nonstationarity

Parameter	d=30		d=50	
	Estimate	S.E.	Estimate	S.E.
α	1.846	0.885	1.775	0.689
q_1	0.937	0.459	0.940	0.376
q_2	0.903	0.443	0.916	0.374
σ_1	1.536	0.659	1.586	0.551
σ_2	1.498	0.619	1.578	0.539

($\delta = 0.5$)

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- The autocorrelation was again $\rho(1, t)$.
- To generate stopping times $\{\tau_{i1}^{(1)}, \tau_{i1}^{(2)}, \tau_{i2}^{(1)}, \tau_{i2}^{(2)}, \cdots, \tau_{ij}^{(1)}, \tau_{ij}^{(2)}, \cdots\}$, we first generated $\tau_{i1}^{(1)}$ based on the conditional distribution of $\tau_{i1}^{(1)} | \tau_{i0}^{(2)}$, then generated $\tau_{i1}^{(2)}$ based on the conditional distribution $\tau_{i1}^{(2)} | \tau_{i1}^{(1)}$, and so on, stopping when the last value was larger than or equal to d.

Other Settings

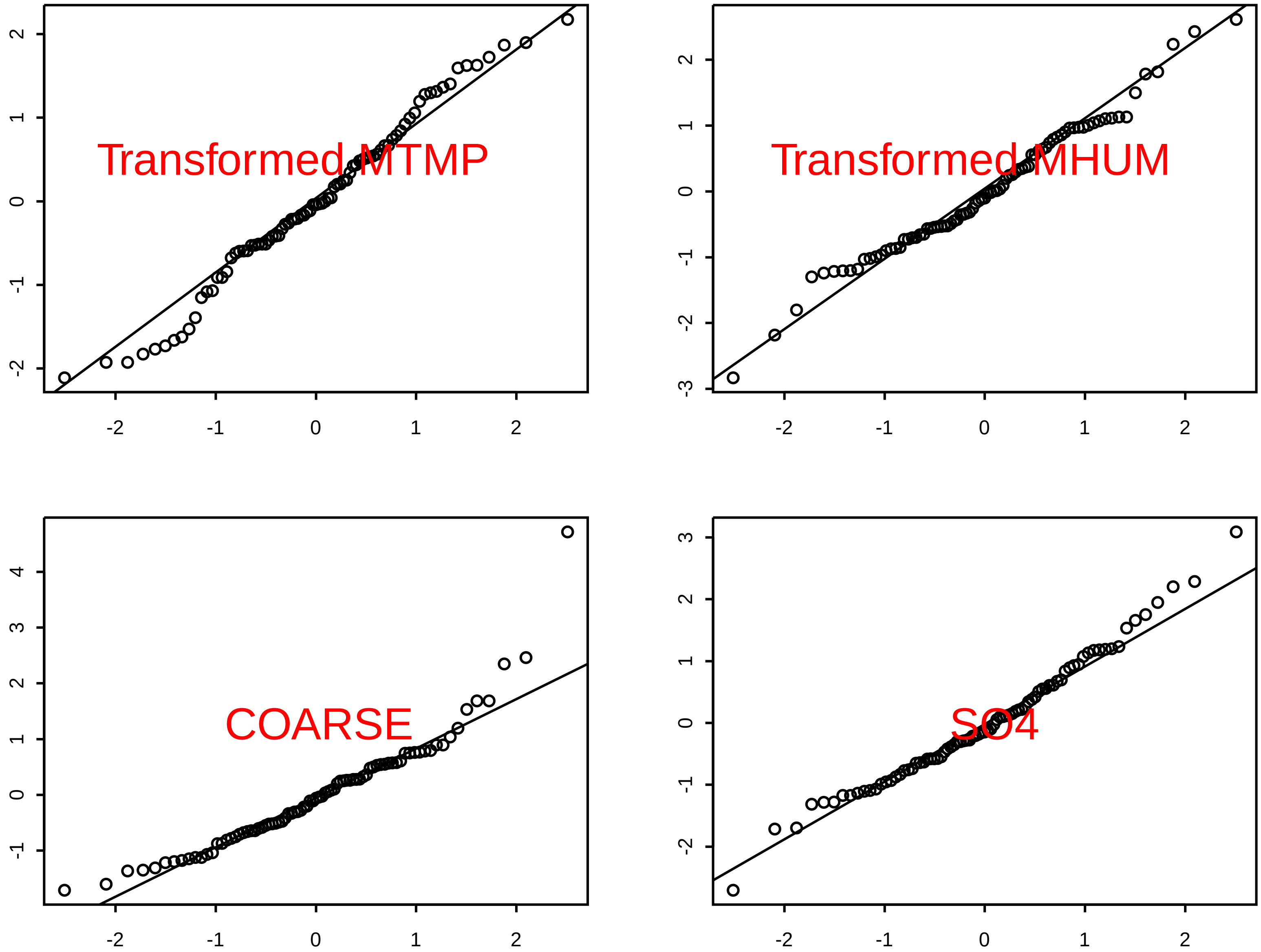
- The simulation was replicated 100 times.
- In each simulation, we used $n = 100$ subjects.
- The number of Gibbs samples depended on the EM iteration and was chosen large enough to minimize numerical differences.
  - It was set at 500, 2000 and 10000 for iterations from 1 to 20, from 20 to 40, and over 40, respectively (Booth and Hobert 1999, McCulloch 1997).
  - The maximum number of EM iterations was set at 100.
- The standard errors of the estimated parameters were calculated using the observed information matrix, based on the formula given by Louis (1982).

Estimation of Covariate Effects

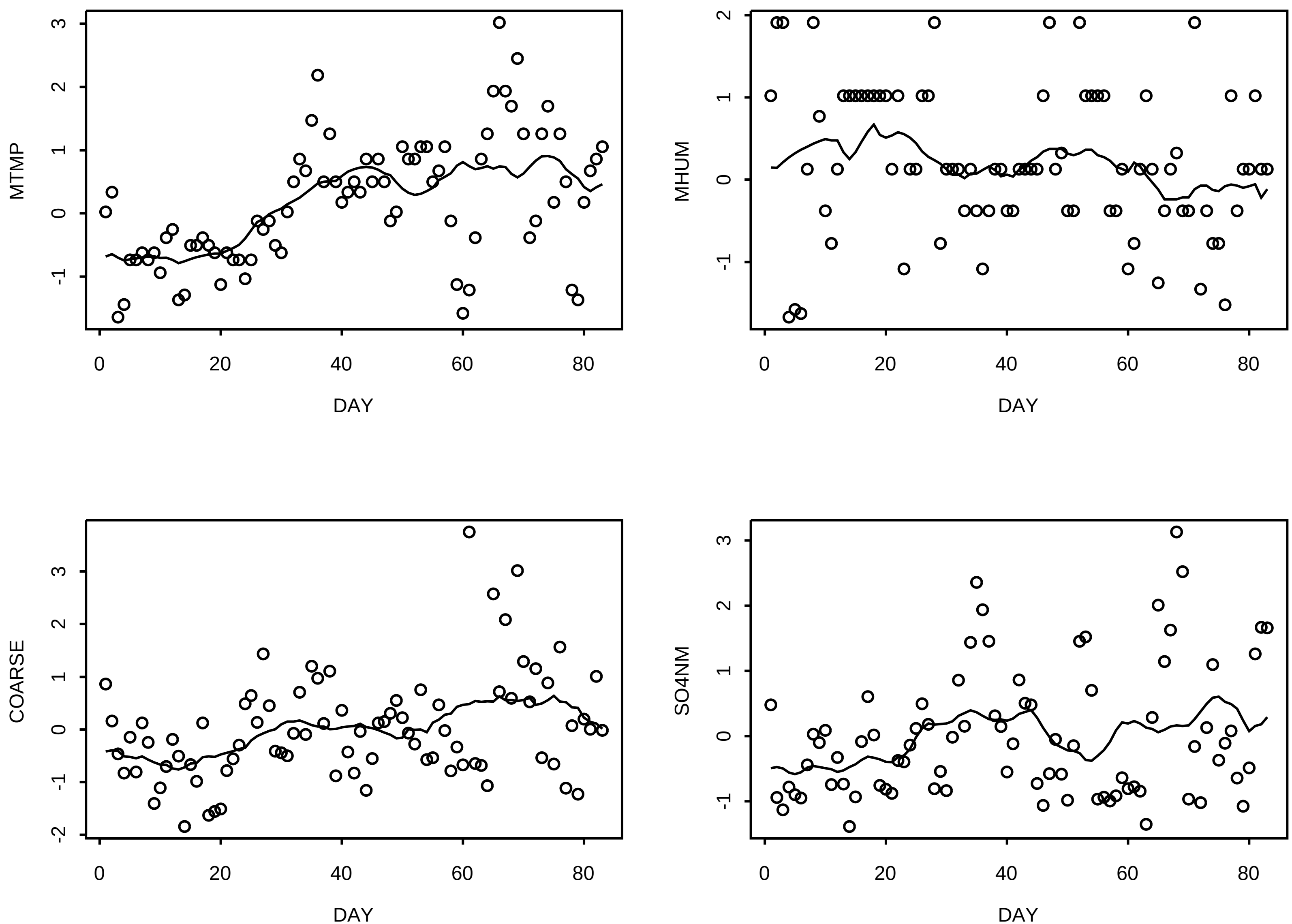
Parameter	True Value	Average	S.E.
γ_{11}	.5	0.43	0.089
γ_{12}	1.0	0.88	0.151
γ_{01}	1.0	0.75	0.095
γ_{02}	1.0	0.81	0.130
β_{11}	-2.5	-2.55	0.236
β_{12}	1.0	0.88	0.334
β_{21}	-4.0	-3.86	0.311
β_{22}	1.5	1.35	0.357

Application

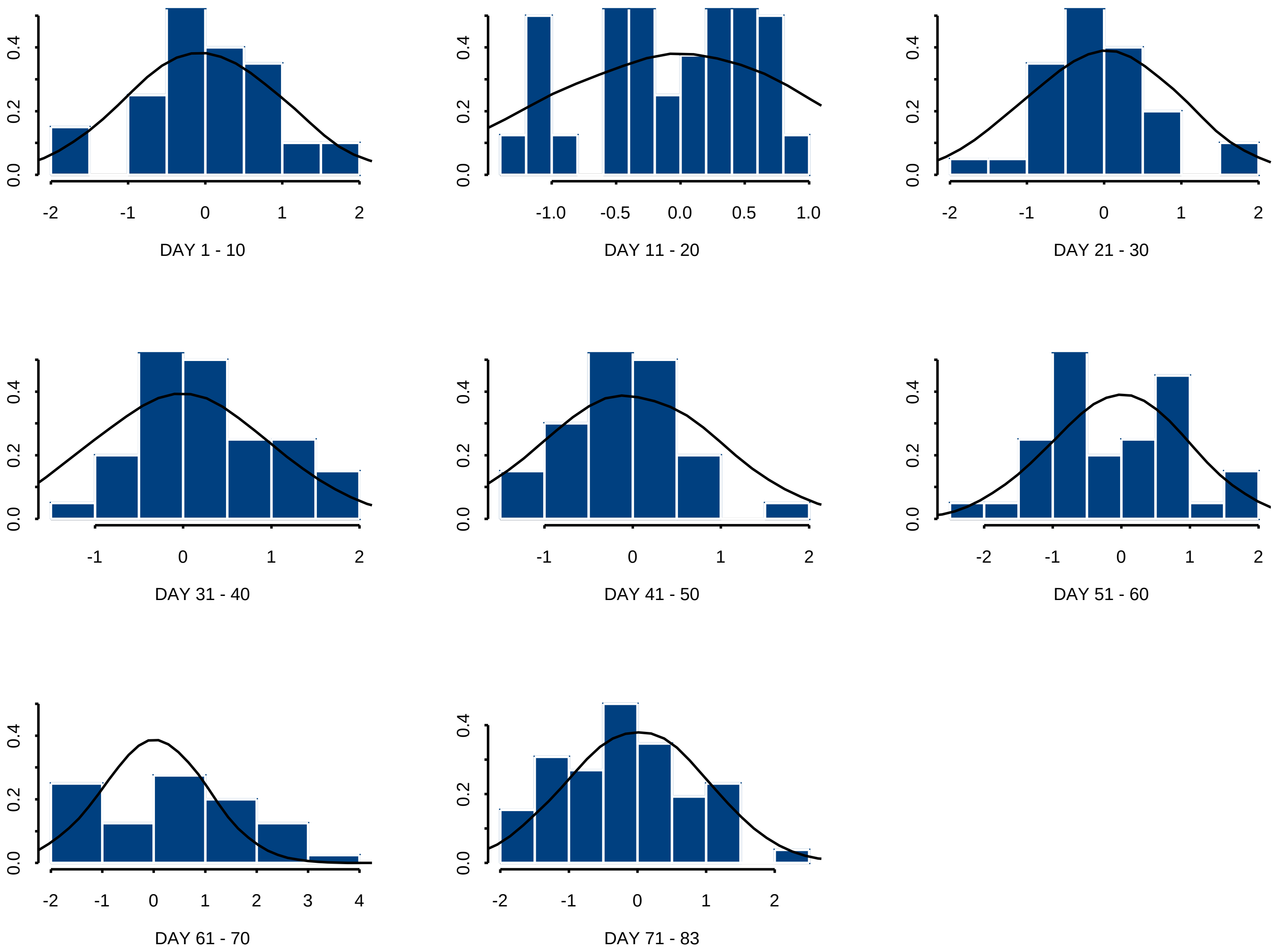
Normality



Air Quality Measures



Residual Plots



Mothers' Predictors for $\lambda_1(t)$

Variable	Runny Nose		Cough	
	Coeff.	SE	Coeff.	SE
$Q_1(t)$	0.025	0.082	-0.043	0.119
U_i	1.092	0.135	1.571	0.199
COARSE	0.404	0.202	0.595	0.285
MTMP	0.146	0.140	0.195	0.195
SO4	0.226	0.238	0.642	0.334
MHUM	-0.644	0.356	-1.029	0.504
ALLERGY	0.598	0.241	0.444	0.354
PETS	0.526	0.244	0.245	0.377
MS	0.584	0.379	0.080	0.515
CHDC	-0.252	0.154	-0.366	0.241

Mothers' Predictors for $\lambda_2(t)$

Variable	Runny Nose		Cough	
	Coeff.	SE	Coeff.	SE
$Q_1(t)$	0.065	0.082	0.074	0.111
U_i	0.004	0.139	0.115	0.163
COARSE	-0.267	0.202	0.228	0.301
MTMP	-0.185	0.147	0.109	0.226
SO4	-0.231	0.252	0.194	0.382
MHUM	0.544	0.358	-0.480	0.527
ALLERGY	-0.255	0.182	0.032	0.262
PETS	0.209	0.172	0.163	0.307
MS	-0.576	0.312	-0.290	0.423
CHDC	0.046	0.133	-0.009	0.214

Infants' Predictors for $\lambda_1(t)$

Variable	Runny Nose		Cough	
	Coeff.	SE	Coeff.	SE
$Q_1(t)$	-0.188	0.081	0.038	0.109
U	0.811	0.107	1.000	0.153
COARSE	-0.159	0.157	-0.425	0.222
MTMP	-0.220	0.107	-0.321	0.151
SO4	-0.419	0.188	-0.653	0.266
MHUM	-0.025	0.284	0.676	0.401
PETS	-0.018	0.176	0.092	0.248
MS	0.372	0.254	-0.341	0.311
CHDC	-0.110	0.109	-0.245	0.159

Infants' Predictors for $\lambda_2(t)$

Variable	Runny Nose		Cough	
	Coeff.	SE	Coeff.	SE
$Q_1(t)$	0.033	0.070	-0.131	0.109
U	0.152	0.076	0.031	0.131
COARSE	0.170	0.156	0.167	0.225
MTMP	0.105	0.110	0.112	0.156
SO4	0.101	0.189	0.079	0.269
MHUM	-0.023	0.285	0.143	0.430
PETS	-0.169	0.138	0.150	0.199
MS	-0.361	0.199	-0.246	0.235
CHDC	0.038	0.098	0.059	0.144

Conclusion

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Such differences reveal not only the sensitivity of the mothers and infants to the air quality, but also call for further understanding of the differences.
It is possible that actions taken to overcome humidity by mothers may inadvertently affect the infants.