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
- Existing Studies of Air Quality
- Limitations of Existing Studies

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

Literature

Model

Estimation

Simulation Study

Application
Significance

- Exposure to ambient pollutants at concentrations above current US Environmental Protection Agency standards is a risk factor for respiratory symptoms, especially in sensitive children.
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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 \( \leq 10 \) microns in diameter (PM\(_{10}\)), particles of mass \( \leq 2.5 \) microns in diameter (PM\(_{2.5}\)), and sulfate (SO\(_{4}^{2-}\)).
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- hospital admissions for respiratory diseases
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- **Zhang et al. (2000) and Gent et al. (2003)**

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General Information

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- Data were collected from 237 mothers and their infants in Southwest Virginia for a summer period from June 10 to August 31, 1995.
- 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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- These variables are denoted by $x_1, \ldots, x_4$, indexed by individual symptom.
## Sample Data

<table>
<thead>
<tr>
<th>DAY</th>
<th>SYMP</th>
<th>MTMP</th>
<th>MHUM</th>
<th>COARSE</th>
<th>SO4</th>
<th>ALL</th>
<th>PETS</th>
<th>CHDC</th>
<th>MS</th>
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<td>208.44</td>
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</tbody>
</table>
## Data Summary

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

* for CHDC > 0.
Background

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Literature

- Limitations of Existing Models
- Zhang et al. (2000) Model
- Joint Models

Model

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Existing models for the data described above are generally restrictive and sometimes involve somewhat arbitrary decisions.
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- Gent et al. (2003) used logistic regression in the context of repeated measures. They used each subject to serve as his or her own control; as a result, personal variables that remained constant during the study could not be included. They also categorized the air quality exposure variables into quintiles for modeling purposes.
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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.
Zhang et al. (2000) Model

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- **✓** enables separate analyses for incidence data, prevalence data, and symptom duration, which are usually difficult to incorporate in a single model
- **✗** air quality measures were included as time-varying covariates ignoring the uncertainties in those repeated measures.
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Tsiatis, Degruittola and Wulfsohn (1995): evaluate the relationship between the repeated measures of CD4 counts and survival. No recurrent event and no multiple repeated measures.
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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

\[ Y_k(t) = \mu_k(t) + W_k(t) \]  \hspace{1cm} (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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\[ W_k(t) = q_kQ(t) + \sigma_k\mathcal{E}_k(t) \]  

(2)

where \( Q(t) \) and \( \mathcal{E}(t) = \{\mathcal{E}_1(t), \ldots, \mathcal{E}_m(t)\} \) 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

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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↓ The reverse \(1 \rightarrow 0\), with event intensity \(\lambda_2(t)\).
Proportional Hazards

For any individual $i$, 

$$
\lambda_i(t) = \exp \{ X_i(t)^T \beta + B_{is}(t) \} \lambda_s, \quad (3)
$$

where 

$$
B_{is}(t) = \gamma_0 U_i + \gamma_s Q(t), \quad (4)
$$

and $\{U_i\}_{i=1}^n$ are subject-specific frailties which follow the standard normal distribution and are independent of $Q(t)$ and $\mathcal{E}(t)$.
We write the $u$-lag correlation functions for $Q(t)$ and $E_k(t)$ as $\rho_1(\alpha_1, u)$ and $\rho_{2k}(\alpha_{2k}, u)$, respectively.
Correlation

We write the \( u \)-lag correlation functions for \( Q(t) \) and \( E_k(t) \) as \( \rho_1(\alpha_1, u) \) and \( \rho_2(\alpha_2, u) \), respectively.

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:

\[
\rho(\alpha, u) = \exp(-\alpha |u|^{\delta}) : 0 < \delta \leq 2.
\] (5)
Covariance-Stationarity

Let
\[ V_1 = \left( \rho_1(\alpha_1, |i - j|) \right)_{d \times d}, \]
where \( \rho_1(\alpha_1, u) \) is defined by (5).
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\[ V_{2k} = \left( \rho_{2k}(\alpha_{2k}, |i - j|) \right)_{d \times d}. \]

\[ \mathcal{E}_k = (\mathcal{E}_k(1), \cdots, \mathcal{E}_k(d))^T \sim N(0, V_{2k}). \]
Let

\[
\begin{aligned}
Y &= (Y_1(1), \ldots, Y_1(d), \ldots, Y_m(1), \ldots, Y_m(d))^T, \\
\mu &= (\mu_1(1), \ldots, \mu_1(d), \ldots, \mu_m(1), \ldots, \mu_m(d))^T.
\end{aligned}
\]
Time Series

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\mu &= (\mu_1(1), \ldots, \mu_1(d), \ldots, \mu_m(1), \ldots, \mu_m(d))^T.
\end{align*}
\]

\(Y \sim d N(\mu, V)\) with

\[
V = \begin{pmatrix}
q_1^2 V_1 + \sigma_{21}^2 V_{21} & q_1 q_2 V_1 & \ldots & q_1 q_m V_1 \\
q_2 q_1 V_1 & q_2^2 V_1 + \sigma_{22}^2 V_{22} & \ldots & q_2 q_m V_1 \\
\vdots & \vdots & \ddots & \vdots \\
q_m q_1 V_1 & q_m q_2 V_1 & \ldots & q_m^2 V_1 + \sigma_{2m}^2 V_{2m}
\end{pmatrix}_{q \times q},
\]

where \(q = d \times m\).
Counting Processes

\[
\begin{align*}
N_i^{(1)}(t) &= \# \{ 0 < u \leq t : Z_i(u) = 1, Z_i(u-) = 0 \}, \\
N_i^{(1)}(0) &= 0,
\end{align*}
\]
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\]

and

\[
\begin{align*}
N_i^{(2)}(t) &= \#\{0 < u \leq t : Z_i(u) = 0, Z_i(u-) = 1\}, \\
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\]
Intensities

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

$$\lambda_i(s)(t) \, dt = \exp\{X_i(t)^T \beta_s + \mathcal{B}_i(s)(t)\} \lambda_s \, dt, \quad (6)$$

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

\[ \tau_{ij}^{(1)} = \inf \{ 0 \leq t \leq T : N_i^{(1)}(t) = j \} \text{ for } 1 \leq j \leq N_i^{(1)}, \]
\[ \tau_{ij}^{(2)} = \inf \{ 0 \leq t \leq T : N_i^{(2)}(t) = j \} \text{ for } 1 \leq j \leq N_i^{(2)}. \]

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

\[ C_{i1} \triangleq \begin{cases} \bigcup_{j=1}^{N_i(1)} (\tau_{i(j-1)}, \tau_{i,j}) \cup \{0\} \cup (\tau_{iN_i(1)}, T] & \text{if } N_i(1) = N_i(2), \\ \bigcup_{j=1}^{N_i(1)} (\tau_{i(j-1)}, \tau_{i,j}) \cup \{0\} & \text{if } N_i(1) = N_i(2) + 1, \end{cases} \]
Partitioning of the Time Interval

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

and

\[ C_{i2} \triangleq \begin{cases} 
\bigcup_{j=1}^{N_i^{(1)}} (\tau_{ij}^{(1)}, \tau_{ij}^{(2)}) & \text{if } N_i^{(1)} = N_i^{(2)}, \\
\bigcup_{j=1}^{N_i^{(2)}} (\tau_{ij}^{(1)}, \tau_{ij}^{(2)}) \cup (\tau_{iN_i^{(1)}}^{(1)}, T] & \text{if } N_i^{(1)} = N_i^{(2)} + 1.
\end{cases} \]
Partitioning of the Time Interval

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

and

\[
C_{i2} \triangleq \begin{cases} 
\bigcup_{j=1}^{N_i^{(1)}} (T_{ij}^{(1)}, T_{ij}^{(2)}) \\
\bigcup_{j=1}^{N_i^{(2)}} (T_{ij}^{(1)}, T_{ij}^{(2)}) \cup (T_{iN_i^{(1)}}, T] & \text{if } N_i^{(1)} = N_i^{(2)}, \\
\bigcup_{j=1}^{N_i^{(1)}} (T_{ij}^{(1)}, T_{ij}^{(2)}) \cup (T_{iN_i^{(1)}}, T] & \text{if } N_i^{(1)} = N_i^{(2)} + 1.
\end{cases}
\]

\[
C_{i1} \cup C_{i2} = [0, T] \text{ and } C_{i1} \cap C_{i2} = \emptyset
\]
Partitioning of the Time Interval

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

and

\[ C_{i2} \triangleq \begin{cases} \bigcup_{j=1}^{N_i(2)} (\tau_{ij}^{(1)}, \tau_{i(j-1)}^{(2)}) \\ \bigcup_{j=1}^{N_i(2)} (\tau_{ij}^{(2)}, \tau_{i(j-1)}^{(1)}) \cup (\tau_{iN_i(2)}^{(1)}, T] & \text{if } N_i^{(1)} = N_i^{(2)}, \\ \bigcup_{j=1}^{N_i(1)} (\tau_{ij}^{(1)}, \tau_{i(j-1)}^{(2)}) \cup (\tau_{iN_i(1)}^{(2)}, T] & \text{if } N_i^{(1)} = N_i^{(2)} + 1. \end{cases} \]

\[ C_{i1} \cup C_{i2} = [0, T] \text{ and } C_{i1} \cap C_{i2} = \emptyset \]

\[ N_i^{(1)} \text{ and } N_i^{(2)} \text{ jump on } C_{i1} \text{ and } C_{i2}, \text{ respectively.} \]
Likelihood Function

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

where
Likelihood Function

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

where

\( \theta \) contains all parameters
Likelihood Function

\[ L(\theta) = L_1(\theta, Y)E_{(Q, U)}[L_2(\theta, N | Q, U)], \quad (7) \]

where

- \( \theta \) contains all parameters
- \( L_1(\theta, Y) \) is the likelihood from the marginal multivariate normal distribution of \( Y \)
Likelihood Function

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

where

- \( \theta \) contains all parameters
- \( L_1(\theta, Y) \) is the likelihood from the marginal multivariate normal distribution of \( Y \)
- \( N = \{(N_i^{(1)}(t), N_i^{(2)}(t)) : 0 < t \leq T\}_{i=1}^{n} \)
Likelihood Function

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

where

- \( \theta \) contains all parameters
- \( L_1(\theta, Y) \) is the likelihood from the marginal multivariate normal distribution of \( Y \)
- \( N = \{(N_i^{(1)}(t), N_i^{(2)}(t)) : 0 < t \leq T\}_{i=1}^{n} \)
- \( U = (U_1, U_2, \ldots, U_n)^T \)
Conditional Likelihood

\[ L_2(\theta, N \mid Q, U) \]

\[ = \left( \prod_{i=1}^{n} \prod_{s=1}^{2} \prod_{t \in C_{is}} \lambda_{is}(t) \Delta N_{i}^{(s)}(t) \right) \times \]

\[ \exp \left[ - \sum_{i=1}^{n} \sum_{s=1}^{2} \int_{0}^{T} \lambda_{is}(t) I(u \in C_{is}) \, du \right] \]

\[ = \left( \prod_{i=1}^{n} \prod_{s=1}^{2} \prod_{t \in C_{is}} \left[ \exp \{ X_{i}^{T}(t) \beta_{s} + B_{is}(t) \} \lambda_{s} \right] \Delta N_{i}^{(s)}(t) \right) \times \]

\[ \exp \left[ - \sum_{i=1}^{n} \sum_{s=1}^{2} \int_{0}^{T} \exp \{ X_{i}^{T}(u) \beta_{s} + B_{is}(u) \} \lambda_{s} I(u \in C_{is}) \, du \right], \]

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

1. Estimate parameters $\alpha_l$, $\alpha_k$, $q_k$ and $\sigma_k$ associated with the time series data $Y$ by maximizing the likelihood function $L_1(\theta, Y)$ in (7).
Two-stage Procedure

1. Estimate parameters $\alpha_1, \alpha_2, q_k$ and $\sigma_{2k}$ associated with the time series data $Y$ by maximizing the likelihood function $L_1(\theta, Y)$ in (7).

2. Treat the maximum likelihood estimates from Stage 1 as if they are known and use the counting processes model (6) to estimate parameters $\beta_s, \gamma_0, \lambda_s (s = 1, 2)$ by maximizing the likelihood function $E_{Q,U|Y}[L_2(\theta, N | Q, U)]$. 
Stage 1

We have $Y \overset{d}{\sim} N(\mu, V)$. 
Stage 1

We have $Y \sim N(\mu, V)$. Then,

$$L_1(\theta, Y) = (2\pi)^{-q} \left[ \det(V) \right]^{-1/2} \exp\left\{-\frac{1}{2}(Y - \mu)^T V^{-1}(Y - \mu)\right\},$$
Stage 1

We have \( Y \sim N(\mu, V) \). Then,

\[
L_1(\theta, Y) = (2\pi)^{-q}[\det(V)]^{-1/2} \exp\left\{ -\frac{1}{2}(Y - \mu)^T V^{-1} (Y - \mu) \right\},
\]

To reduce computational complexity, we can pre-estimate \( \mu \) by a weighted moving average,

\[
\hat{\mu}_k(t) = \sum_{s=-m_0}^{m_0} w(s) Y_k(t + s)
\]  

(8)

for pre-specified non-zero weights

\( \{w(s) : s = -m_0, -m_0 + 1, \cdots, 0, \cdots, m_0 - 1, m_0\} \).
We use the EM algorithm (Dempster, Laird and Rubin, 1977) to maximize

\[ E_{(Q,U)|Y} \left[ L_2(\theta, N \mid Q, U) \right]. \]
Stage 2

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

$$E_{(Q,U)\mid Y}[L_2(\theta, N \mid Q, U)].$$

$Q$ and $U$ are the unobserved data and $N$ is observed, so the complete likelihood is the joint density of $(N, Q, U)$. 
Stage 2

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

\[ E_{(Q,U)|Y} \left[ L_2(\theta, N \mid Q, U) \right]. \]

\(Q\) and \(U\) are the unobserved data and \(N\) is observed, so the complete likelihood is the joint density of \((N, Q, U)\). The EM algorithm starts with an initial value \(\theta^{(0)}\), and then evaluates the expectation of the log likelihood of \((Q, U)\) conditional on \(N\), denoted by \(E_{\theta^{(0)}} \left[ l_2(\theta, N, Q, U) \mid N \right]. \)
Stage 2

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

$$E_{(Q,U)|Y} \left[ L_2(\theta, N | Q, U) \right].$$

$Q$ and $U$ are the unobserved data and $N$ is observed, so the complete likelihood is the joint density of $(N, Q, U)$.

The EM algorithm starts with an initial value $\theta^{(0)}$, and then evaluates the expectation of the log likelihood of $(Q, U)$ conditional on $N$, denoted by $E_{\theta^{(0)}} [L_2(\theta, N, Q, U)|N]$. This expectation involves integral of $U = \{U_i\}_{i=1}^{83}$ and $Q$, where $U$ is subject specific frailty and $Q$ is random process.
Stage 2

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

\[ E_{(Q,U)|Y} \left[ L_2(\theta, N | Q, U) \right]. \]

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The EM algorithm starts with an initial value \( \theta^{(0)} \), and then evaluates the expectation of the log likelihood of \((Q, U)\) conditional on \( N \), denoted by \( E_{\theta^{(0)}} [l_2(\theta, N, Q, U)|N] \).

- This expectation involves integral of \( U = \{U_i\}_{i=1}^{83} \) and \( Q \), where \( U \) is subject specific frailty and \( Q \) is random process.
- Gibbs sampler is used to approximate this high dimensional integral.
Stage 2

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

$$E_{(Q,U)\mid Y} [L_2(\theta, N \mid Q, U)].$$

$Q$ and $U$ are the unobserved data and $N$ is observed, so the complete likelihood is the joint density of $(N, Q, U)$.

The EM algorithm starts with an initial value $\theta^{(0)}$, and then evaluates the expectation of the log likelihood of $(Q, U)$ conditional on $N$, denoted by $E_{\theta^{(0)}} [l_2(\theta, N, Q, U)\mid N]$.

- This expectation involves integral of $U = \{U_i\}_{i=1}^{83}$ and $Q$, where $U$ is subject specific frailty and $Q$ is random process.

- Gibbs sampler is used to approximate this high dimensional integral.

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

Stage 1: Time Series Model
- Effect of Correlation Parameter $\delta = 0.5$
- Effect of Correlation Parameter $\delta = 2$
- Effect of Nonstationarity
  Parameter Estimates under Nonstationarity

Stage 2: Counting Processes
- Other Settings
- Estimation of Covariate Effects

Application
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.
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.
- The model for $Y_k$ is $Y_k(t) = \mu_k(t) + q_k Q(t) + q_k \mathcal{E}_k(t)$. 
Stage 1: Time Series Model

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- The model for $Y_k$ is $Y_k(t) = \mu_k(t) + q_k Q(t) + q_k \varepsilon_k(t)$.

- We used the correlation families (5). To demonstrate that assuming $\delta = 1$ for the modeling has only a small effect on the estimation, we generated data with the true $\delta$ taking values 0.5 and 2.0.
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.

- The model for $Y_k$ is $Y_k(t) = \mu_k(t) + q_k Q(t) + q_k E_k(t)$.

- We used the correlation families (5). To demonstrate that assuming $\delta = 1$ for the modeling has only a small effect on the estimation, we generated data with the true $\delta$ taking values 0.5 and 2.0.

- Each simulation was replicated 1000 times.
## Effect of Correlation Parameter $\delta = .5$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>True Value</th>
<th>$d=30$</th>
<th></th>
<th>$d=50$</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimate</td>
<td>S.E.</td>
<td>Estimate</td>
<td>S.E.</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.81</td>
<td>1.375</td>
<td>1.732</td>
<td>1.081</td>
<td>0.622</td>
</tr>
<tr>
<td>$q_1$</td>
<td>1.0</td>
<td>0.916</td>
<td>0.130</td>
<td>0.935</td>
<td>0.102</td>
</tr>
<tr>
<td>$q_2$</td>
<td>1.0</td>
<td>0.908</td>
<td>0.131</td>
<td>0.940</td>
<td>0.104</td>
</tr>
</tbody>
</table>
Effect of Correlation Parameter $\delta = 2$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>True Value</th>
<th>d=30</th>
<th>d=50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimate</td>
<td>S.E.</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.81</td>
<td>0.971</td>
<td>0.334</td>
</tr>
<tr>
<td>$q_1$</td>
<td>1.0</td>
<td>0.962</td>
<td>0.138</td>
</tr>
<tr>
<td>$q_2$</td>
<td>1.0</td>
<td>0.956</td>
<td>0.132</td>
</tr>
</tbody>
</table>
Effect of Nonstationarity

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

\[ Y_k(t) = \mu_k(t) + q_k Q(t) + \sigma(t) E_k(t), \tag{9} \]

where \( Q(t) \) and \( E_k(t) \) are independent stationary Gaussian processes, whilst the function \( \sigma(t) \) was generated from the \( \chi^2_1 \) distribution at the discrete time points to introduce the nonstationarity for \( Y_k(t) \).
Effect of Nonstationarity

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

\[ Y_k(t) = \mu_k(t) + q_k Q(t) + \sigma(t) E_k(t), \]  

(9)

where \( Q(t) \) and \( E_k(t) \) are independent stationary Gaussian processes, whilst the function \( \sigma(t) \) was generated from the \( \chi^2_1 \) 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 \( \alpha \) under the stationary assumption.
### Parameter Estimates under Nonstationarity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( d = 30 )</th>
<th>S.E.</th>
<th>( d = 50 )</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>1.846</td>
<td>0.885</td>
<td>1.775</td>
<td>0.689</td>
</tr>
<tr>
<td>( q_1 )</td>
<td>0.937</td>
<td>0.459</td>
<td>0.940</td>
<td>0.376</td>
</tr>
<tr>
<td>( q_2 )</td>
<td>0.903</td>
<td>0.443</td>
<td>0.916</td>
<td>0.374</td>
</tr>
<tr>
<td>( \sigma_1 )</td>
<td>1.536</td>
<td>0.659</td>
<td>1.586</td>
<td>0.551</td>
</tr>
<tr>
<td>( \sigma_2 )</td>
<td>1.498</td>
<td>0.619</td>
<td>1.578</td>
<td>0.539</td>
</tr>
</tbody>
</table>

\( \delta = 0.5 \)
Stage 2: Counting Processes

- $X_1 \equiv 1$ and $X_2 \sim Uniform(0, 1)$. 
Stage 2: Counting Processes

- $X_1 \equiv 1$ and $X_2 \sim Uniform(0, 1)$.

- The counting processes $N^{(1)}$ and $N^{(2)}$ were generated with intensities $\lambda_1(t)$ and $\lambda_2(t)$ defined by (3) and (4), respectively.
Stage 2: Counting Processes

- $X_1 \equiv 1$ and $X_2 \sim \text{Uniform}(0, 1)$.
- The counting processes $N^{(1)}$ and $N^{(2)}$ were generated with intensities $\lambda_1(t)$ and $\lambda_2(t)$ defined by (3) and (4), respectively.
- The autocorrelation was again $\rho(1, t)$. 
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- The counting processes $N^{(1)}$ and $N^{(2)}$ were generated with intensities $\lambda_1(t)$ and $\lambda_2(t)$ defined by (3) and (4), respectively.

- The autocorrelation was again $\rho(1, t)$.

- To generate stopping times $
  \{\tau_{i1}^{(1)}, \tau_{i1}^{(2)}, \tau_{i2}^{(1)}, \tau_{i2}^{(2)}, \ldots, \tau_{ij}^{(1)}, \tau_{ij}^{(2)}, \ldots\} \}$, 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>True Value</th>
<th>Average</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma_{11}$</td>
<td>.5</td>
<td>0.43</td>
<td>0.089</td>
</tr>
<tr>
<td>$\gamma_{12}$</td>
<td>1.0</td>
<td>0.88</td>
<td>0.151</td>
</tr>
<tr>
<td>$\gamma_{01}$</td>
<td>1.0</td>
<td>0.75</td>
<td>0.095</td>
</tr>
<tr>
<td>$\gamma_{02}$</td>
<td>1.0</td>
<td>0.81</td>
<td>0.130</td>
</tr>
<tr>
<td>$\beta_{11}$</td>
<td>$-2.5$</td>
<td>$-2.55$</td>
<td>0.236</td>
</tr>
<tr>
<td>$\beta_{12}$</td>
<td>1.0</td>
<td>0.88</td>
<td>0.334</td>
</tr>
<tr>
<td>$\beta_{21}$</td>
<td>$-4.0$</td>
<td>$-3.86$</td>
<td>0.311</td>
</tr>
<tr>
<td>$\beta_{22}$</td>
<td>1.5</td>
<td>1.35</td>
<td>0.357</td>
</tr>
</tbody>
</table>
Application
Background
Yale Mothers and Infants Health (YMIH) Study
PI: Brian Leaderer, Ph.D.

Literature
Model
Estimation
Simulation Study

Application
- Normality
- Air Quality Measures
- Residual Plots
- Mothers’ Predictors for $\lambda_1(t)$
- Mothers’ Predictors for $\lambda_2(t)$
- Infants’ Predictors for $\lambda_1(t)$
- Infants’ Predictors for $\lambda_2(t)$
- Conclusion

Normality

Transformed MTMP

Transformed MHUM

COARSE

SO4
Residual Plots

DAY 1 - 10
DAY 11 - 20
DAY 21 - 30
DAY 31 - 40
DAY 41 - 50
DAY 51 - 60
DAY 61 - 70
DAY 71 - 83
Mothers’ Predictors for $\lambda_1(t)$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Runny Nose</th>
<th>Cough</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coeff.</td>
<td>SE</td>
</tr>
<tr>
<td>$Q_1(t)$</td>
<td>0.025</td>
<td>0.082</td>
</tr>
<tr>
<td>$U_i$</td>
<td>1.092</td>
<td>0.135</td>
</tr>
<tr>
<td>COARSE</td>
<td>0.404</td>
<td>0.202</td>
</tr>
<tr>
<td>MTMP</td>
<td>0.146</td>
<td>0.140</td>
</tr>
<tr>
<td>SO4</td>
<td>0.226</td>
<td>0.238</td>
</tr>
<tr>
<td>MHUM</td>
<td>-0.644</td>
<td>0.356</td>
</tr>
<tr>
<td>ALLERGY</td>
<td>0.598</td>
<td>0.241</td>
</tr>
<tr>
<td>PETS</td>
<td>0.526</td>
<td>0.244</td>
</tr>
<tr>
<td>MS</td>
<td>0.584</td>
<td>0.379</td>
</tr>
<tr>
<td>CHDC</td>
<td>-0.252</td>
<td>0.154</td>
</tr>
</tbody>
</table>
Mothers’ Predictors for $\lambda_2(t)$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Runny Nose</th>
<th>Cough</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coeff.</td>
<td>SE</td>
</tr>
<tr>
<td>$Q_1(t)$</td>
<td>0.065</td>
<td>0.082</td>
</tr>
<tr>
<td>$U_i$</td>
<td>0.004</td>
<td>0.139</td>
</tr>
<tr>
<td>COARSE</td>
<td>-0.267</td>
<td>0.202</td>
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<tr>
<td>MTMP</td>
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<td>0.147</td>
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<tr>
<td>SO4</td>
<td>-0.231</td>
<td>0.252</td>
</tr>
<tr>
<td>MHUM</td>
<td>0.544</td>
<td>0.358</td>
</tr>
<tr>
<td>ALLERGY</td>
<td>-0.255</td>
<td>0.182</td>
</tr>
<tr>
<td>PETS</td>
<td>0.209</td>
<td>0.172</td>
</tr>
<tr>
<td>MS</td>
<td>-0.576</td>
<td>0.312</td>
</tr>
<tr>
<td>CHDC</td>
<td>0.046</td>
<td>0.133</td>
</tr>
</tbody>
</table>
## Infants’ Predictors for $\lambda_1(t)$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Runny Nose</th>
<th>Cough</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coeff.</td>
<td>SE</td>
</tr>
<tr>
<td>$Q_1(t)$</td>
<td>-0.188</td>
<td>0.081</td>
</tr>
<tr>
<td>$U$</td>
<td>0.811</td>
<td>0.107</td>
</tr>
<tr>
<td>COARSE</td>
<td>-0.159</td>
<td>0.157</td>
</tr>
<tr>
<td>MTMP</td>
<td>-0.220</td>
<td>0.107</td>
</tr>
<tr>
<td>SO4</td>
<td>-0.419</td>
<td>0.188</td>
</tr>
<tr>
<td>MHUM</td>
<td>-0.025</td>
<td>0.284</td>
</tr>
<tr>
<td>PETS</td>
<td>-0.018</td>
<td>0.176</td>
</tr>
<tr>
<td>MS</td>
<td>0.372</td>
<td>0.254</td>
</tr>
<tr>
<td>CHDC</td>
<td>-0.110</td>
<td>0.109</td>
</tr>
</tbody>
</table>
## Infants’ Predictors for $\lambda_2(t)$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Runny Nose</th>
<th>Cough</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coeff.</td>
<td>SE</td>
</tr>
<tr>
<td>$Q_1(t)$</td>
<td>0.033</td>
<td>0.070</td>
</tr>
<tr>
<td>$U$</td>
<td>0.152</td>
<td>0.076</td>
</tr>
<tr>
<td>COARSE</td>
<td>0.170</td>
<td>0.156</td>
</tr>
<tr>
<td>MTMP</td>
<td>0.105</td>
<td>0.110</td>
</tr>
<tr>
<td>SO4</td>
<td>0.101</td>
<td>0.189</td>
</tr>
<tr>
<td>MHUM</td>
<td>-0.023</td>
<td>0.285</td>
</tr>
<tr>
<td>PETS</td>
<td>-0.169</td>
<td>0.138</td>
</tr>
<tr>
<td>MS</td>
<td>-0.361</td>
<td>0.199</td>
</tr>
<tr>
<td>CHDC</td>
<td>0.038</td>
<td>0.098</td>
</tr>
</tbody>
</table>
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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.
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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.