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Structural Modelling of Nonlinear Exposure-Response Relationships for Longitudinal Data

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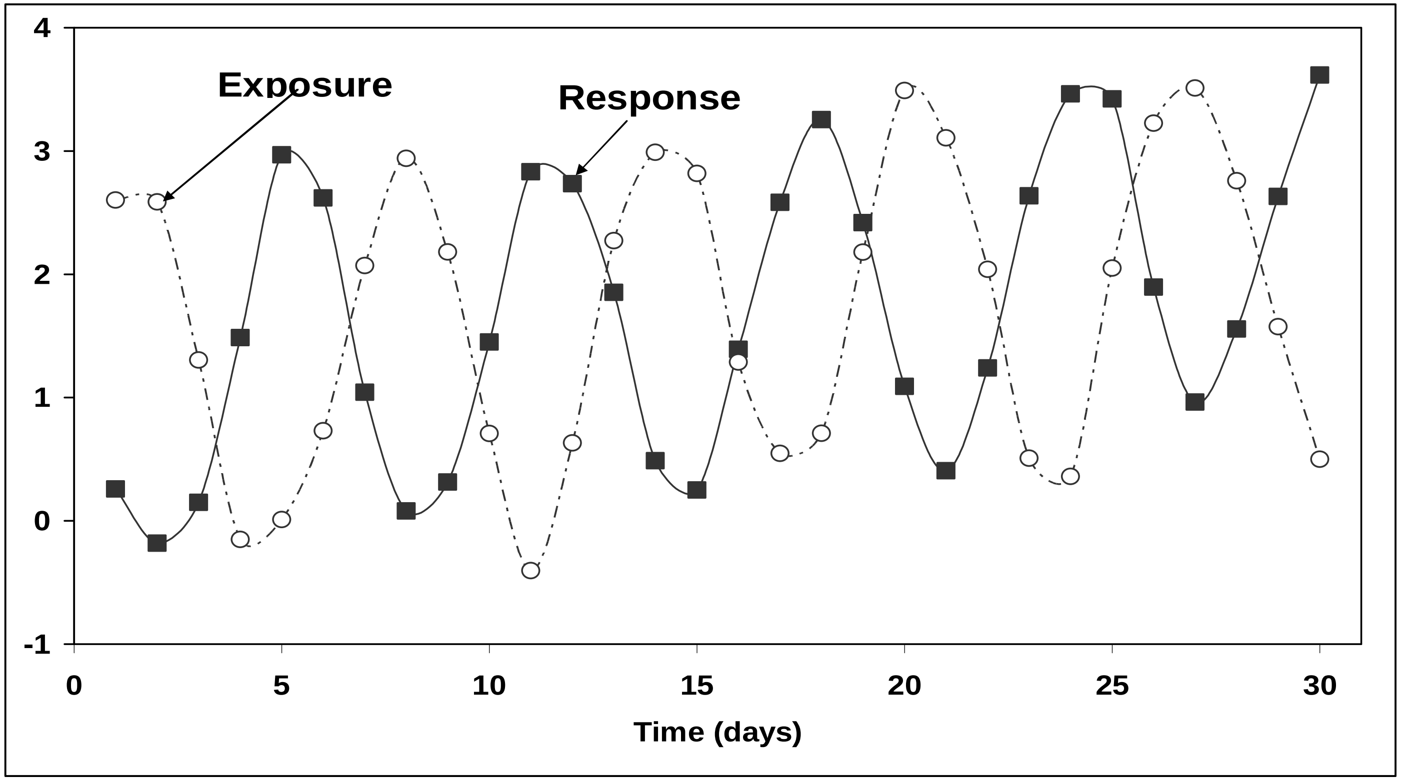
- **Background**
- **Mathematical Model**
- **Model Validity and Illustration**
- **Conclusions**

Background

- Many research is grounded on exposure and risk assessment
- Linear model often used to assess exposure-response relationship
- Standard methods provide few theories for nonlinear exposure-response studies
- See an example in the following



Linear mixed-effects model shows parameter estimate of -0.61 is statistically discernible at 5% level. Response is negatively associated with exposure which is incorrect.

Mathematical Model

- Model equations
- Model estimation

Model Equations

- Methodological framework for model buildup

- Model is quivalent to a mixed-effects model

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Model Buildup

- Let $\{x\}_t$ and $\{y\}_t$ be exposure and response measures for any subject
- Use Hodrick-Prescott (HP) filter technique to extract the trend-cycle component
- Obtain structural mapping of exposure to response for individual subject
- Extend the mapping to group subjects by adding random subject effects

Model Equations

$$y_t = y^{trend}{}_t + \varepsilon_y{}^{trend}{}_t \quad (1)$$

$$y_{trend}{}^{t+1} = 2\, y_{trend}{}^{t} - y_{trend}{}^{t\text{-}1} + \varepsilon_y{}^{cycle}{}_t \quad (2)$$

similarly

$$x_t = x^{trend}{}_t + \varepsilon_x{}^{trend}{}_t \quad (3)$$

$$x_{trend}{}^{t+1} = 2\, x_{trend}{}^{t} - x_{trend}{}^{t\text{-}1} + \varepsilon_x{}^{cycle}{}_t \quad (4)$$

$$y_t = x_t\alpha + \sum(t - j)\eta_j$$

Where $\eta_t \sim \mathbf{N}(0, \sigma_\eta^2)$

This is for individual subject

$$y_{it} = x_{it}\alpha + x_{it}u_i + \sum(t - j)\eta_j + \varepsilon_{it}$$

Where $\varepsilon_{it} \sim N(0, \sigma_\varepsilon^2)$

This is for group subjects where u_i is inserted to account for subject-specific variation from the group mean

In matrix form (mixed-effects model)

$$Y = Xa + Z_u u + Z_\eta \eta + \varepsilon$$

$$\begin{bmatrix} u \\ \eta \\ \varepsilon \end{bmatrix} = N(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \Sigma_u & 0 & 0 \\ 0 & \Sigma_\eta & 0 \\ 0 & 0 & \Sigma_\varepsilon \end{bmatrix})$$

$$\Sigma_u = \sigma_u^2 I, \ \Sigma_\varepsilon = \sigma_\varepsilon^2 I$$

$$\boldsymbol{V} = \mathrm{Var}(\boldsymbol{Y}) = \sigma_u^2 \mathbf{Z}_u \mathbf{Z}_u^T + \mathbf{Z}_\eta \Sigma_\eta \mathbf{Z}_\eta^T + \sigma_\varepsilon^2 \boldsymbol{I}$$

Model Estimation

- If V is known the estimates are the best linear unbiased predictors (BLUPs) of the model
- If V is unknown the estimates of parameters and V are jointly using iterative methods
- In SAS's MIXED procedure, for example, modified Newton-Raphson method is adopted

Model Validity and Illustration

- Consider the hypothetical data in Fig. 1
- Define y_t as the response and x_t the time-varying exposure at the *t*th day
- The proposed model has the following exposure-response form

$$y^{trend}_t = a_0 + a_1 x^{trend}_t + \varepsilon_t$$

where y^{trend}_t and x^{trend}_t are calculated according to HP decomposition

Results and comparison of model fit to the hypothetical data

	Response		
	Proposed model	Linear mixed-effects model	$Pr > \chi^2$
Exposure (a_1)	1.86***	-0.61***	
AIC (smaller better)	-6.3	89.7	***

p***<0.001; p**<0.005; p*<0.1

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Conclusions

- Exposure measures are common in many fields
- We present some ways to structural modelling nonlinear longitudinal data that can not easily be modeled by traditional statistical methods
- The proposed approach includes the deseasoning method as a special case which is often limited to a time series only.
- The developed model is computationally attractive as various software packages and routines exist to perform the final obtained mixed-effects model


Thank You For Your Attention