

A Bayesian multi-dimensional couple-based latent risk model for infertility

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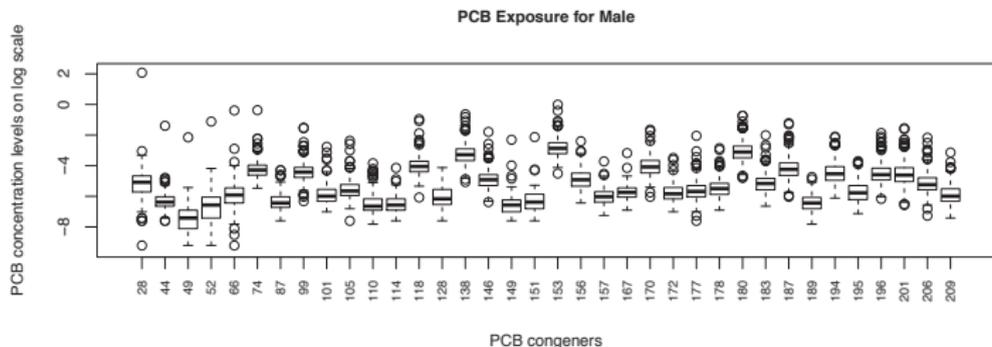
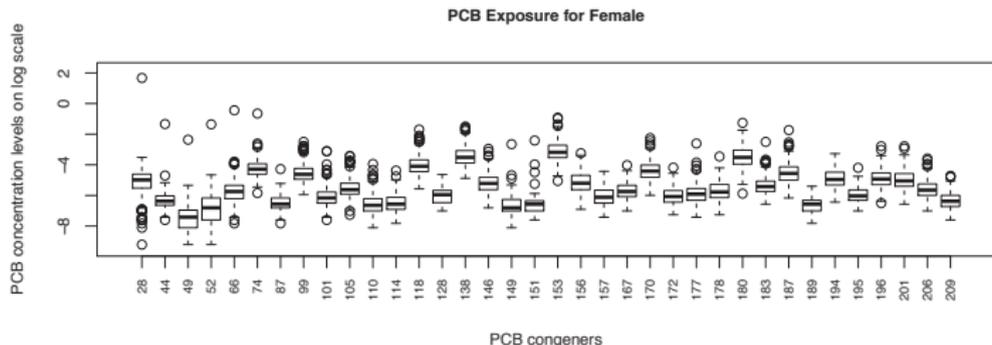
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(A joint work with Beom Seuk Hwang, Germaine M. Buck Louis, and Paul S. Albert)

Longitudinal Investigation of Fertility and the Environment (LIFE) Study (Buck Louis et al., 2011)

- ▶ 501 couples enrolled; 401 followed up for 12 cycles; 347 achieved pregnancy and 54 did not
- ▶ Infertility: no pregnancy after 12 menstrual cycles
- ▶ 36 polychlorinated biphenyl (PCB) congeners for both partners of the couple
- ▶ Primary aim: Assess the effects of environmental chemicals on infertility from a couple-based perspective

Boxplots of positive PCB congeners on log scale in the LIFE Study



Descriptive Statistics of Covariates in the LIFE Study

Table 1: Descriptive statistics of covariates on the original scale in the LIFE Study.

Covariate	Female			Male		
	Mean	Med	SD	Mean	Med	SD
Age(years)	29.8	29	4.0	31.7	31	4.7
Serum lipids(<i>ng/g</i>)	616.3	603.1	115.9	731.6	687.4	216.3
Serum cotinine(<i>ng/mL</i>)	14.0	0.02	59.61	48.0	0.036	131.4

Covariate	Level	Female	Male
		N(%)	N(%)
BMI (<i>kg/m²</i>)	< 25	186(49.2)	69(18.3)
	25-30	97(25.7)	151(39.9)
	≥ 30	95(25.1)	158(41.8)

Several Challenges

- ▶ Couple-based design: With both partners of a couple considered, it is necessary to consider complex interactions between the exposure patterns for each of the two partners.
- ▶ High-dimensional biomarker data: With 72 PCBs, traditional statistical models may fail to assess the collective association between chemical exposures and risk of infertility.
- ▶ Semicontinuous biomarker data: about 25% PCBs are zeros; need to be modeled through a mixture of a degenerate distribution at zero and a continuous distribution for nonzero values.

Previous Work: Zhang, Chen and Albert (*Biostatistics*, 2012)

- ▶ Zhang, Chen and Albert (2012) investigated the relationship between environmental PCB exposures and the risk of endometriosis.
- ▶ Proposed a joint latent class model with random effects.
- ▶ Considered the complex association between mean of PCBs and zero probability of PCBs.
- ▶ Only female's PCBs are considered.

Objectives and Approach

► Objectives

- Propose a Bayesian high-dimensional couple-based latent class approach for estimating the associations between environmental chemical mixtures and the risk of infertility.

► Approach

- Link the complex chemical mixtures of each couple and infertility risk through unobserved latent classes.
- Latent classes are linked to the risk of infertility through a logistic model with main and interaction effects between latent classes.
- Introduce dependence structures between the chemical mixture patterns within a couple and between the chemical patterns and the risk of infertility.

Notation

- ▶ Let Y_i be a binary variable indicating fertility or infertility for the i th couple, $i = 1, \dots, I$, where $Y_i = 1$ denotes infertility and $Y_i = 0$ denotes fertility.
- ▶ Let X_{ij}^F and X_{ij}^M be the concentrations of the j th PCB exposure measured in serum for female and male partners, respectively in the i th couple, $j = 1, \dots, J$.
- ▶ Each X_{ij} can be represented by two variables: for $i = 1, \dots, I, j = 1, \dots, J$,

$$U_{ij}^F = \begin{cases} 1, & \text{if } X_{ij}^F \neq 0 \\ 0, & \text{if } X_{ij}^F = 0 \end{cases} \quad \text{and} \quad V_{ij}^F = \begin{cases} X_{ij}^F, & \text{if } X_{ij}^F \neq 0 \\ \text{irrelevant}, & \text{if } X_{ij}^F = 0 \end{cases}$$

$$U_{ij}^M = \begin{cases} 1, & \text{if } X_{ij}^M \neq 0 \\ 0, & \text{if } X_{ij}^M = 0 \end{cases} \quad \text{and} \quad V_{ij}^M = \begin{cases} X_{ij}^M, & \text{if } X_{ij}^M \neq 0 \\ \text{irrelevant}, & \text{if } X_{ij}^M = 0 \end{cases}$$

where U_{ij}^F and U_{ij}^M are the binary nonzero PCB value indicators for females and males, respectively, and V_{ij}^F and V_{ij}^M are the nonzero values of the PCB exposures.

Latent Risk Classes

- ▶ Let L_i^F and L_i^M be the latent class variables for females and males, where L_i^F (L_i^M) takes the value k ($k = 0, \dots, K - 1$) if female (male) in the i th couple belongs to class k .
 - Assume the latent class has higher risk of infertility as k increases.
 - For example, the 3-latent class model is composed of low-risk class ($L_i = 0$), medium-risk class ($L_i = 1$) and high-risk class ($L_i = 2$).
- ▶ Latent class models

$$\begin{aligned}\pi_k^F &= Pr(L_i^F = k) \\ \pi_k^M &= Pr(L_i^M = k),\end{aligned}$$

Infertility Model

- ▶ Probability distribution of infertility of couple i given the latent class variables:

$$\text{logit}P(Y_i = 1|L_i^F, L_i^M) = \beta_0 + \beta_1^F L_i^F + \beta_1^M L_i^M + \beta_2 L_i^F L_i^M,$$

- β_0 : the log odds of infertility when both partners are in the lowest risk classes.
- β_1^F : the change of the log odds of infertility from a female's risk class to the next higher risk class given the corresponding male belongs to the lowest risk class.
- To solve "label switching" problem, an inequality constraint was imposed: $\beta_1^F > 0$ and $\beta_1^M > 0$.
- β_2 : how differences in log odds between two adjacent females' latent classes are different depending on what risk classes the corresponding males belong to.
- $\beta_2 > 0$: synergistic effect; $\beta_2 < 0$: subadditivity effect of risk classes between females and males.

Chemical Concentration Model

- ▶ Log-normal distribution of the nonzero values of PCB exposures, V_{ij}^F and V_{ij}^M :

$$V_{ij}^F | L_{ij}^F, \mathbf{b}_j^F \sim \text{logN}(\mu_{ij}^F(L_i^F, \mathbf{b}_j^F), \tau_F^2),$$

$$V_{ij}^M | L_{ij}^M, \mathbf{b}_j^M \sim \text{logN}(\mu_{ij}^M(L_i^M, \mathbf{b}_j^M), \tau_M^2)$$

with $\mu_{ij}^F(L_i^F, \mathbf{b}_j^F)$ and τ_F^2 denoting the mean and variance of V_{ij}^F on the log scale.

- ▶ The means of the nonzero PCB exposures, $\mu_{ij}^F(L_i^F, \mathbf{b}_j^F)$ and $\mu_{ij}^M(L_i^M, \mathbf{b}_j^M)$:

$$\mu_{ij}^F(L_i^F, \mathbf{b}_j^F) = \alpha_0^F + \alpha_1^F L_i^F + b_{0j}^F + b_{1j}^F L_i^F,$$

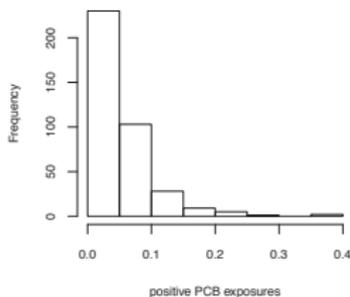
$$\mu_{ij}^M(L_i^M, \mathbf{b}_j^M) = \alpha_0^M + \alpha_1^M L_i^M + b_{0j}^M + b_{1j}^M L_i^M,$$

- The latent class variables allow the PCBs from the same participant to be correlated, and the random effects allow for each PCB to have varying departures from the overall mean.

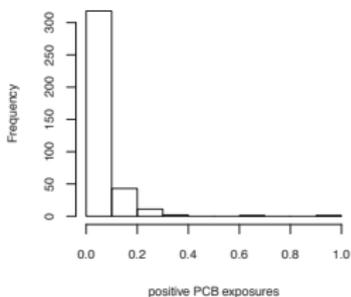
- ▶ $\mathbf{b}_j = (b_{0j}^F, b_{1j}^F, b_{0j}^M, b_{1j}^M)' \sim N_4(\mathbf{0}, \Sigma_b)$.

Histograms of PCB congener 153 in the LIFE Study

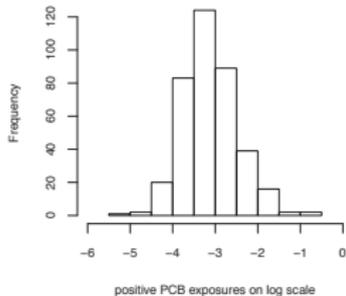
(a) Histogram of PCB congener 153 in Females



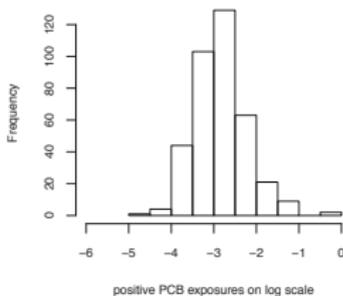
(b) Histogram of PCB congener 153 in Males



(c) Histogram of PCB congener 153 in Females on log scale



(d) Histogram of PCB congener 153 in Males on log scale

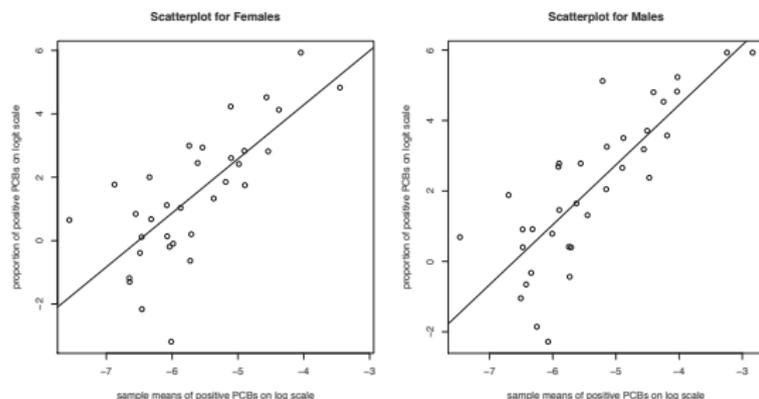


Chemical Concentration Model (Cont.)

- ▶ The probability of nonzero PCB exposures is associated with the mean of nonzero PCB values:

$$\text{logit}P(U_{ij}^F = 1|L_i^F, \mathbf{b}_j^F) = \eta_0^F + \eta_1^F h(\mu_{ij}^F(L_i^F, \mathbf{b}_j^F)),$$
$$\text{logit}P(U_{ij}^M = 1|L_i^M, \mathbf{b}_j^M) = \eta_0^M + \eta_1^M h(\mu_{ij}^M(L_i^M, \mathbf{b}_j^M)),$$

where function $h(\cdot)$ is specified as the identity function based on data structure.



Complete Data Likelihood

- The complete data likelihood is given by

$$\begin{aligned} L &= \prod_{i=1}^I \left(\frac{e^{\Lambda_i}}{1 + e^{\Lambda_i}} \right)^{y_i} \left(\frac{1}{1 + e^{\Lambda_i}} \right)^{1-y_i} \times \pi_{L_i^F}^F \times \pi_{L_i^M}^M \\ &\times \prod_{i=1}^I \prod_{j=1}^J \left(\frac{e^{\eta_0^F + \eta_1^F \mu_{ij}^F(\cdot)}}{1 + e^{\eta_0^F + \eta_1^F \mu_{ij}^F(\cdot)}} \right)^{u_{ij}^F} \left(\frac{1}{1 + e^{\eta_0^F + \eta_1^F \mu_{ij}^F(\cdot)}} \right)^{1-u_{ij}^F} \\ &\times \prod_{i=1}^I \prod_{j=1}^J \left(\frac{e^{\eta_0^M + \eta_1^M \mu_{ij}^M(\cdot)}}{1 + e^{\eta_0^M + \eta_1^M \mu_{ij}^M(\cdot)}} \right)^{u_{ij}^M} \left(\frac{1}{1 + e^{\eta_0^M + \eta_1^M \mu_{ij}^M(\cdot)}} \right)^{1-u_{ij}^M} \\ &\times \prod_{i=1}^I \prod_{j=1}^J \left[\log N(v_{ij}^F; \mu_{ij}^F(L_i^F, \mathbf{b}_j^F), \tau_F^2) \right]^{u_{ij}^F} \times \left[\log N(v_{ij}^M; \mu_{ij}^M(L_i^M, \mathbf{b}_j^M), \tau_M^2) \right]^{u_{ij}^M} \\ &\times \prod_{j=1}^J N_4(\mathbf{b}_j; \mathbf{0}, \Sigma_b), \end{aligned}$$

where $\Lambda_i = \beta_0 + \beta_1^F L_i^F + \beta_1^M L_i^M + \beta_2 L_i^F L_i^M$.

Covariates Dependence

- ▶ Subject-specific covariates can be incorporated into the model:

$$V_{ij}^F | L_i^F, \mathbf{b}_j^F, \mathbf{W}_i^F \sim \log N(\mu_{ij}^F(L_i^F, \mathbf{b}_j^F, \mathbf{W}_i^F), \tau_F^2)$$

$$V_{ij}^M | L_i^M, \mathbf{b}_j^M, \mathbf{W}_i^M \sim \log N(\mu_{ij}^M(L_i^M, \mathbf{b}_j^M, \mathbf{W}_i^M), \tau_M^2)$$

and

$$\text{logit}P(U_{ij}^F = 1 | L_i^F, \mathbf{b}_j^F, \mathbf{W}_i^F) = \eta_0^F + \eta_1^F h(\mu_{ij}^F(L_i^F, \mathbf{b}_j^F, \mathbf{W}_i^F))$$

$$\text{logit}P(U_{ij}^M = 1 | L_i^M, \mathbf{b}_j^M, \mathbf{W}_i^M) = \eta_0^M + \eta_1^M h(\mu_{ij}^M(L_i^M, \mathbf{b}_j^M, \mathbf{W}_i^M))$$

where the conditional means of the nonzero PCB exposures are expressed as

$$\mu_{ij}^F(L_i^F, \mathbf{b}_j^F, \mathbf{W}_i^F) = \alpha_0^F + \alpha_1^F L_i^F + b_{0j}^F + b_{1j}^F L_i^F + \mathbf{W}_i^{F'} \boldsymbol{\lambda}^F$$

$$\mu_{ij}^M(L_i^M, \mathbf{b}_j^M, \mathbf{W}_i^M) = \alpha_0^M + \alpha_1^M L_i^M + b_{0j}^M + b_{1j}^M L_i^M + \mathbf{W}_i^{M'} \boldsymbol{\lambda}^M$$

where \mathbf{W}_i^F and \mathbf{W}_i^M are vectors of subject-specific covariates such as age, BMI or smoking status, and $\boldsymbol{\lambda}^F$ and $\boldsymbol{\lambda}^M$ are parameter vectors for females and males, respectively.

- ▶ MCMC algorithm consisting of Gibbs sampling and adaptive Metropolis algorithm.
- ▶ Model comparison
 - Use a modified deviance information criterion (DIC) by Celeux et al. (2006).

$$\text{DIC}_4 = -4E_{\theta, Z}[\log f(y, Z|\theta)|y] + 2E_Z[\log f(y, Z|E_{\theta}[\theta|y, Z])|y]$$

where $f(y, Z|\theta)$ is the complete likelihood, y is the observed data and Z are the random effects and latent variables.

Results in the LIFE Data Analysis

- ▶ To establish the best model, let the number of risk classes varies between 2 and 5 for both partners.
- ▶ The 5-class model for both partners fits the data best.

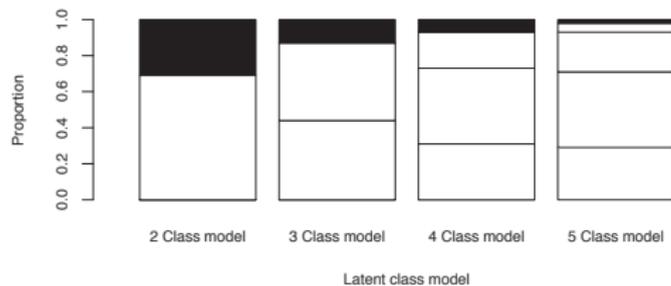
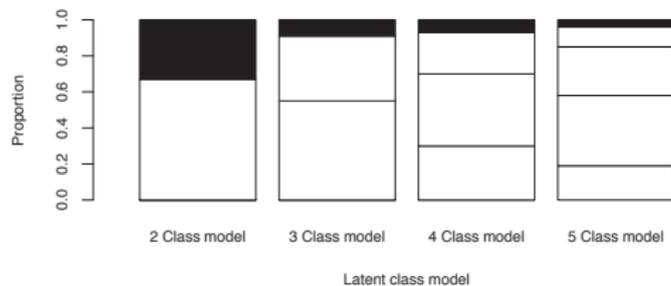
Table 2: Estimated DICs with different numbers of classes in the LIFE Study

		Males			
Number of Classes		2	3	4	5
Females	2	-154854.4	-155840.2	-156309.4	-156533.8
	3	-155773.8	-156761.7	-157286.4	-157472.6
	4	-156332.2	-157338.5	-157850.1	-158121.7
	5	-156550.0	-157524.8	-158048.8	-158296.9

Results: Posterior means and 95% credible intervals for some parameters

Para.	2-class model	3-class model	4-class model	5-class model
β_0	-1.99(-2.39,-1.64)	-2.12(-2.59,-1.71)	-2.30(-2.92,-1.79)	-2.32(-2.96,-1.77)
β_1^F	0.59(0.14,1.20)	0.46(0.11,0.97)	0.41(0.11,0.83)	0.34(0.09,0.70)
β_1^M	0.48(0.11,1.04)	0.46(0.11,0.91)	0.44(0.12,0.88)	0.47(0.13,0.91)
β_2	-1.14(-2.32,-0.10)	-0.53(-1.06,-0.06)	-0.31(-0.62,-0.05)	-0.27(-0.52,-0.06)
α_0^F	-5.91(-6.29,-5.53)	-5.97(-6.35,-5.58)	-6.20(-6.59,-5.81)	-6.27(-6.66,-5.89)
α_1^F	0.70(0.60,0.80)	0.57(0.48,0.66)	0.46(0.38,0.54)	0.41(0.34,0.48)
α_0^M	-5.54(-5.93,-5.14)	-5.65(-6.04,-5.25)	-5.79(-6.18,-5.40)	-5.83(-6.22,-5.44)
α_1^M	0.63(0.53,0.73)	0.56(0.48,0.64)	0.45(0.37,0.53)	0.43(0.35,0.51)
ρ_{01}^{FF}	0.26(-0.08,0.56)	0.18(-0.15,0.49)	0.09(-0.24,0.41)	0.11(-0.23,0.42)
ρ_{00}^{FM}	0.97(0.94,0.98)	0.97(0.94,0.98)	0.97(0.94,0.98)	0.97(0.94,0.98)
ρ_{01}^{FM}	0.19(-0.15,0.49)	0.10(-0.23,0.41)	0.11(-0.21,0.42)	0.10(-0.24,0.42)
ρ_{10}^{FM}	0.32(-0.01,0.60)	0.23(-0.10,0.53)	0.14(-0.18,0.45)	0.16(-0.17,0.47)
ρ_{11}^{FM}	0.55(0.29,0.75)	0.45(0.14,0.68)	0.39(0.08,0.64)	0.35(0.04,0.61)
ρ_{01}^{MM}	0.25(-0.08,0.54)	0.15(-0.18,0.46)	0.16(-0.17,0.47)	0.15(-0.18,0.45)

Results: Barplots of the estimated class membership probabilities



Results: 5-class Model

- ▶ The odds of infertility are about 40% ($=\exp(\beta_1^F=0.34)$) higher when the female partner of the couple moves to a higher risk class, if the male partner is in the lowest risk class ($L_i^M = 0$).
- ▶ The odds of infertility are about 60% ($=\exp(\beta_1^M=0.47)$) higher when the male partner of the couple moves to a higher risk class, if the female partner is in the lowest risk group ($L_i^F = 0$).
- ▶ However, the negative estimate of the interaction effect ($\hat{\beta}_2 = -0.27$) suggests that a couple's risk of infertility does not necessarily go up when one partner moves to a higher risk class, implying a subadditivity effect.
- ▶ Positive α_1^F and α_1^M : Higher-risk classes are more likely to have large mean values of nonzero PCB exposures than lower-risk classes.
- ▶ There are strong positive correlations between female and male partners, in both random intercepts ($\rho_{00}^{FM} = 0.97$) and slopes ($\rho_{11}^{FM} = 0.36 \sim 0.55$).

- ▶ Data were generated from 2- and 3-class joint models with a single covariate.
- ▶ 100 datasets were generated for each scenario.
- ▶ Simulation Scenarios
 - Scenario I: Both female and male partners can be grouped into 2 latent risk classes.
 - Scenario II: Both female and male partners grouped into 3 latent risk classes.
 - Scenario III: Females grouped into 2 latent classes, while males grouped into 3.

Table 3: Simulation results of Scenario I: Adjusted joint models fit to data generated assuming 2 latent classes for each partner.

Para.	Truth	2-class model	3-class model	4-class model	5-class model
β_0	-2.5	-2.70(-3.12,-2.22)	-2.70(-3.11,-2.21)	-2.70(-3.11,-2.22)	-2.70(-3.12,-2.21)
β_1^F	0.5	0.69(0.38,1.26)	0.69(0.37,1.28)	0.69(0.37,1.25)	0.69(0.38,1.26)
β_1^M	0.5	0.70(0.38,1.22)	0.70(0.38,1.19)	0.70(0.39,1.20)	0.70(0.38,1.23)
β_2	1	0.82(0.04,1.39)	0.81(0.02,1.37)	0.81(0.04,1.38)	0.81(0.05,1.39)
α_0^F	-6	-6.01(-6.34,-5.68)	-6.01(-6.34,-5.68)	-6.01(-6.34,-5.68)	-6.01(-6.34,-5.67)
α_1^F	1	1.02(0.66,1.37)	1.02(0.67,1.38)	1.02(0.67,1.37)	1.02(0.67,1.37)
α_0^M	-6	-5.97(-6.27,-5.65)	-5.97(-6.27,-5.65)	-5.97(-6.27,-5.65)	-5.97(-6.27,-5.65)
α_1^M	1	1.03(0.71,1.37)	1.03(0.71,1.37)	1.03(0.71,1.37)	1.03(0.71,1.37)
ρ_{01}^{FF}	0	0.01(-0.33,0.31)	0.01(-0.33,0.31)	0.01(-0.33,0.31)	0.01(-0.33,0.31)
ρ_{00}^{FM}	0	0.01(-0.28,0.34)	0.01(-0.28,0.34)	0.01(-0.28,0.34)	0.01(-0.28,0.34)
ρ_{01}^{FM}	0	-0.01(-0.32,0.27)	-0.01(-0.33,0.27)	-0.01(-0.33,0.27)	-0.01(-0.32,0.27)
ρ_{10}^{FM}	0	0.01(-0.35,0.33)	0.01(-0.35,0.33)	0.01(-0.35,0.34)	0.01(-0.35,0.33)
ρ_{11}^{FM}	0	0.03(-0.27,0.39)	0.03(-0.27,0.38)	0.03(-0.27,0.38)	0.03(-0.27,0.38)
ρ_{01}^{MM}	0	0.01(-0.37,0.33)	0.01(-0.37,0.33)	0.01(-0.37,0.33)	0.01(-0.36,0.33)
DIC		-179158.1	-179154.8	-179151.2	-179146.2

Table 4: Simulation results of Scenario II: Adjusted joint models fit to data generated assuming 3 latent classes for each partner.

Para.	Truth	2-class model	3-class model	4-class model	5-class model
β_0	-4.5	-5.56(-9.74,-3.97)	-5.15(-6.73,-4.07)	-5.16(-6.79,-4.09)	-5.15(-6.74,-4.08)
β_1^F	0.5	1.30(0.59,3.19)	0.79(0.42,1.54)	0.80(0.42,1.51)	0.79(0.42,1.41)
β_1^M	0.5	1.16(0.59,2.85)	0.77(0.40,1.35)	0.78(0.40,1.42)	0.77(0.41,1.41)
β_2	1	2.53(1.51,5.85)	0.90(0.54,1.29)	0.89(0.54,1.27)	0.90(0.56,1.27)
α_0^F	-6	-5.99(-6.36,-5.59)	-5.99(-6.37,-5.60)	-5.99(-6.36,-5.60)	-5.99(-6.36,-5.60)
α_1^F	1	1.53(1.08,1.99)	1.01(0.72,1.32)	1.01(0.72,1.32)	1.01(0.72,1.32)
α_0^M	-6	-6.00(-6.38,-5.69)	-6.01(-6.39,-5.70)	-6.01(-6.39,-5.70)	-6.01(-6.39,-5.70)
α_1^M	1	1.55(1.13,2.01)	1.02(0.73,1.33)	1.02(0.73,1.33)	1.02(0.73,1.33)
ρ_{01}^{FF}	0	-0.03(-0.30,0.31)	-0.03(-0.31,0.30)	-0.03(-0.31,0.30)	-0.03(-0.31,0.30)
ρ_{00}^{FM}	0	0.01(-0.34,0.36)	0.01(-0.34,0.36)	0.01(-0.33,0.36)	0.01(-0.34,0.36)
ρ_{01}^{FM}	0	0.03(-0.30,0.35)	0.03(-0.30,0.35)	0.03(-0.30,0.35)	0.03(-0.30,0.35)
ρ_{10}^{FM}	0	-0.01(-0.31,0.32)	-0.01(-0.29,0.32)	-0.01(-0.29,0.32)	-0.01(-0.30,0.32)
ρ_{11}^{FM}	0	0.02(-0.28,0.35)	0.02(-0.27,0.33)	0.02(-0.27,0.33)	0.02(-0.26,0.33)
ρ_{01}^{MM}	0	-0.001(-0.31,0.35)	-0.004(-0.31,0.34)	-0.003(-0.31,0.34)	-0.003(-0.31,0.34)
DIC		-136709.0	-148858.8	-148856.5	-148849.9

Table 5: Simulation results of Scenario III: Estimated DICs in the adjusted joint models assuming different numbers of risk classes when the true model has 2 latent classes for females and 3 latent classes for males.

Number of Classes		Males	
		2	3
Females	2	-158154.2	-164270.2
	3	-158152.7	-164266.9

Results: Simulation Studies

► Scenario I:

- The DIC suggests that the 2-class model is the best for this generated data.
- All the parameters have very similar estimates and are close to the truth.
- The robustness of the parameter inferences may not be surprising, given very small prevalence of higher risk classes in higher class models.

► Scenario II:

- The 3-, 4- and 5-class models all have estimates that are close to the truth, while the 2-class model has biased estimates in some parameters, especially in β 's, τ 's and σ^2 's.
- The 3-class model has the lowest DIC, indicating that its performance is the best.

► Scenario III:

- The 2/3-class model has the smallest DIC, followed closely by the 3/3-class model, while the 2/2- and 3/2-class models have higher DIC values.
- The estimates from the 2/2- and 3/2-class models are also biased.

Conclusions

- ▶ Proposed a Bayesian joint latent class model of high-dimensional chemical exposures and the risk of infertility.
- ▶ Exposures to a collection of PCB congeners are linked to the risk of infertility through the latent risk classes of both partners of the couple.
- ▶ The latent class variables allow the risk of infertility to differ across the classes, and differ between the two partners of a couple.
- ▶ The model takes into account the correlated exposure patterns of both partners of the couple while considering the complex interactions between them.
- ▶ The male PCB exposure needs to be carefully considered in assessing the effect of environmental contaminants on infertility ($\beta_1^F = 0.34$ and $\beta_1^M = 0.47$).
- ▶ The negative interaction suggests that once one partner of the couple has a high risk chemical exposure pattern, then the other partner's risk profile does not increase the risk of infertility.

Future Work

- ▶ When longitudinal data are available on the chemical exposures, a dynamic modeling framework can be constructed where the latent risk classes can follow a Markov process with distinctive transition probabilities (hidden Markov models).
- ▶ It is also possible to let the latent risk class to depend on subject- or couple-specific covariates.
- ▶ Treat them as discrete if the linearity assumption is deemed inappropriate or as continuous if it is believed a large number of latent classes exist.
- ▶ Mediating effects (semens, menstrual cycle characteristics, etc.)