A Bayesian Growth Mixture Model to Examine Maternal Hypertension and Birth Outcomes

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Gestational Blood Pressure and Birth Outcomes

- Hypertension in pregnancy is associated with a number of adverse birth outcomes, including
  - Preterm birth (PTB)
  - Low birth weight (LBW)
  - Restricted fetal growth

Gestational Blood Pressure

- In healthy pregnant women, blood pressure is U-shaped over the course of pregnancy
  - Declines until mid-gestation, then rises until delivery

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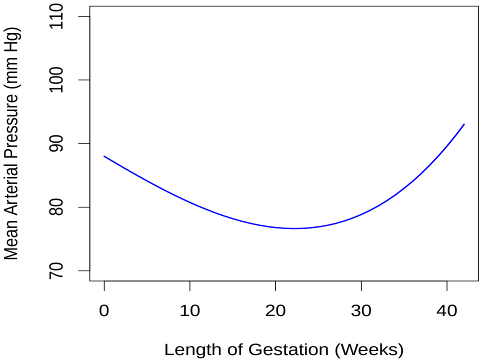
Fig. 1: Typical gestational blood pressure trajectory.



Gestational Blood Pressure and Birth Outcomes

- In contrast, in women who are at increased risk for adverse birth outcomes, blood pressure remains elevated throughout pregnancy

- Elevated blood pressure more likely in
  - Women over age 35
  - Non-Hispanic blacks
  - Primiparous women

- Clinical relevance: By monitoring blood pressure during pregnancy, obstetric providers can identify women at risk for adverse outcomes and intervene with appropriate treatments

Research Questions

- Research question 1: Can we identify distinct patient subpopulations, each characterized by an average blood pressure trajectory over the course of pregnancy?
- Research question 2: Are these blood pressure trajectories associated with birth outcomes?

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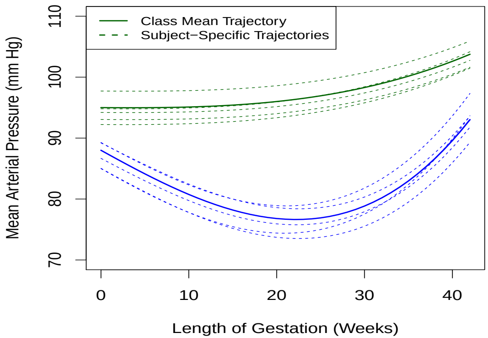
Fig. 2: Two hypothetical patient subgroups.



Healthy Pregnancy, Healthy Baby (HPHB) Study

- Our analysis is based on data from the Healthy Pregnancy, Healthy Baby (HPHB) Study
    - Prospective cohort study examining how individual, social and environmental factors influence pregnancy outcomes
    - Part of the EPA-funded Southern Center for Environmentally Driven Disparities in Birth Outcomes
    - Enrolls pregnant women from Duke University Obstetrics Clinic and the Durham County Health Department Prenatal Clinic

HPHB Study

- Patient interviews and medical record reviews were used to obtain
  - Demographic information
  - Medical history
  - Blood pressure measurements from routine prenatal visits
- Maternal blood samples collected at 28 weeks to assess environmental exposures
- Birth outcomes recorded at delivery

HPHB Study

- Data analysis limited to:
  - Non-Hispanic white and non-Hispanic black mothers
  - Singleton gestation with delivery between 28–42 weeks
  - No history of chronic hypertension

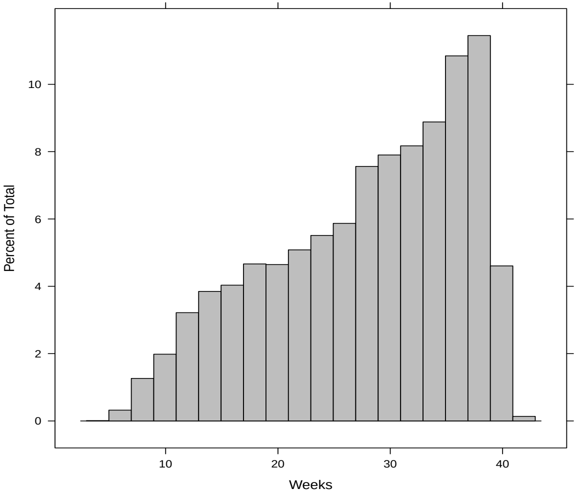
HPHB Patient Characteristics

Table 1: Characteristics of HPHB Study participants ($n = 1027$).

Variable	%
Preterm Birth	13
Low Birth Weight	12
Maternal Race	
Non-Hispanic white	22
Non-Hispanic black	78
Maternal Age	
18–20 years	25
21–34 years	64
$\geq$ 35 years	11
Maternal Education	
$>$ High school	47
$\leq$ High school	53
Parity	
Primiparous	42
Multiparous	58
Insurance Status	
Private	23
Other	77
	Mean (SD)
Serum Cotinine (ng/mL)	19.44 (52.17)
Mean Arterial Pressure (mm Hg)	88.0 (9.13)

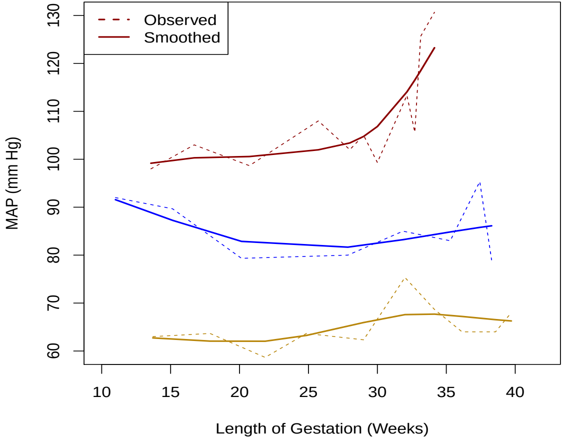
Histogram of Prenatal Visits

Fig. 3: Histogram of Prenatal Visits ($N = 10,290$).



MAP Curves for Three Study Participants

Fig. 4: Raw and smoothed MAP curves for 3 study participants.



Modeling Strategy: Bayesian Growth Mixture Model (GMM)

- Growth Mixture Model (Verbeke and Lesaffre, 1996; Muthén and Shedden, 1999)
  - Finite mixture of random effects models
  - Assumes that subjects first fall into one of a small number of latent classes
  - Each class defined by an average trajectory or "growth curve"
  - Around these class means, subjects have their own unique trajectories defined by a set of random effects
- Resource: Frühwirth-Schnatter, S. (2006). *Finite Mixture and Markov Switching Models*. Springer: New York.

Model Specification in 4 Steps

Step 1: Specify a growth mixture model for MAP

$$
\begin{aligned}
f(y_{ij}|\mathbf{b}_i) &= \sum_{k=1}^{K} \pi_{ik}(\mathbf{w}_i)\mathrm{N}(y_{ij}; \eta_{ijk}, \sigma_k^2) \\
&= \sum_{k=1}^{K} \Pr(C_i = k; \mathbf{w}_i)\mathrm{N}(y_{ij}; \eta_{ijk}, \sigma_k^2); \\
\eta_{ijk} &= \mathbf{t}_{ij}'\boldsymbol{\beta}_k + \mathbf{v}_{ij}'\mathbf{b}_i
\end{aligned}
$$

where:

- y_{ij} = MAP measurement at the j-th visit for patient i
- $\pi_{ik}(\mathbf{w}_i) = \Pr(\text{patient } i \in \text{class } k)$
- C_i = unobserved class-indicator variable
- $\mathbf{b}_i | C_i = k \sim \mathrm{N}(\mathbf{0}, \boldsymbol{\Sigma}_k)$

Step 2: Link to Birth Outcomes

Step 2: Link MAP trajectories to PTB (z_1) and LBW (z_2)

$$f(y_{ij}, z_{1i}, z_{2i} | \mathbf{b}_i; \mathbf{w}_i, \mathbf{t}_{ij}, \mathbf{v}_{ij}) = \sum_{k=1}^{K} \pi_{ik}(\mathbf{w}_i) \mathrm{N}(y_{ij}; \eta_{ijk}, \sigma_k^2) \times p(z_{1i}, z_{2i}; \psi_k)$$

- Given $C_i = k$, PTB and LBW are *conditionally independent* of MAP
  - $(z_{1i}, z_{2i}) \perp\!\!\!\perp y_{ij} | C_i \quad \forall i, j$
- However, PTB and LBW are *conditionally correlated* given class membership
- So we allow a "residual" dependence b/w PTB and LBW

Step 3: Bivariate Probit Model for PTB and LBW

Step 3: Specify a bivariate probit model for $p(z_{1i}, z_{2i}; \psi_k)$

- Introduce underlying normal variables, z^*_{1i} and z^*_{2i}
- $z_{1i} = 1$ if $z^*_{1i} > 0$ and $z_{2i} = 1$ if $z^*_{2i} > 0$

$$\left(\begin{array}{c} z^*_{1i} \\ z^*_{2i} \end{array} \right) \Big| C_i = k \;\sim\; \mathrm{N}_2\left(\boldsymbol{\mu}_k, \mathbf{R}_k\right) = \mathrm{N}_2\left[\left(\begin{array}{c} \mu_{1k} \\ \mu_{2k} \end{array} \right), \left(\begin{array}{cc} 1 & \rho_k \\ \rho_k & 1 \end{array} \right) \right]$$

- Allows us to compute joint probabilities of PTB and LBW for each class
- ρ_k is class-specific correlation between PTB and LBW
- An aside: Could allow $\boldsymbol{\mu}_k$ to be a function of covariates

Final Step: Multinomial Logit Model for Class-Membership Probabilities

Step 4: Link class-membership probabilities to patient covariates (age, race, serum cotinine, etc.) via multinomial logit model:

$$\Pr(C_i = k) = \pi_{ik}(\mathbf{w}_i) \;=\; \frac{e^{\mathbf{w}_i'\gamma_k}}{\sum_{h=1}^{K} e^{\mathbf{w}_i'\gamma_h}}, \text{ with } \gamma_1 = 0.$$

- $\mathbf{w}_i$ = vector of patient-level predictors
- γ = vector of regression parameters
- K = number of blood pressure trajectory classes (≥ 2)

Parameter Estimation

- Maximum Likelihood Estimation: EM algorithm (Mplus, R Flexmix)
- Bayesian Estimation:
  - Place prior distributions on model parameters
  - Use Markov chain Monte Carlo (MCMC) to draw from joint posterior
- Priors:
  - Normal priors for $\boldsymbol{\beta}_k$
  - Inverse-gamma/Inverse-Wishart priors for variances
  - Normal priors for $\boldsymbol{\mu}_k$
  - U(-1,1) priors for ρ_k
  - N$(\mathbf{0}, (9/4)\mathbf{I})$ for class-membership parameters, $\boldsymbol{\gamma}_k$ (Garrett and Zeger, 2000)
    - Centers $\pi_{ik}(\mathbf{w}_i)$'s at $1/K$ and bounds them away from 0 and 1

Posterior Computation

- Data-augmentation approach
  - Draw class-membership parameters, $\boldsymbol{\gamma}_k \, (k = 2, \ldots, K)$
  - For each subject, compute posterior class-membership probabilities $\Pr(C_i = k | \mathbf{y}_i)$
  - Draw C_i from multinomial logit
  - Using data for subjects assigned to class k, update class-k parameters ($\boldsymbol{\beta}_k$, $\boldsymbol{\mu}_k$, etc.)
- In our case, all full conditionals have closed forms except:
  - γ_k = Class-membership regression parameters
  - ρ_k = Bivariate probit correlation parameter
  - Used random-walk Metropolis-Hastings

Modeling Selection Strategy

- How many classes?
- Let number of classes K range from $1, 2, \ldots, K_{\text{max}}$
- Use Deviance Information Criterion (DIC) to choose the optimal model (Spiegelhalter et al., 2002)

$$\text{DIC} = \overline{D} + p_D$$

  - Assessment of model fit + penalty for model complexity
  - Smaller values are better

- We use a modified DIC for finite mixture models (Celeux et al., 2006)

Model Selection Results

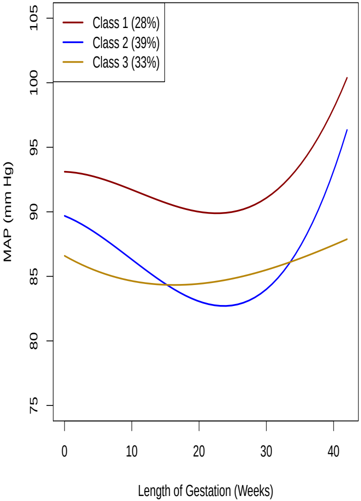
Table 2: Model comparison statistics for HPHB Study.

Number of Classes (K)	Model Description	DIC
1	Cubic Fixed Effects	75743
	Random Intercept	67296
	Random Intercept and Slope	66473
2	Cubic Fixed Effects	71268
	Random Intercept	66912
	Random Intercept and Slope	65942
3	Cubic Fixed Effects	69809
	Random Intercept	66393
	Random Intercept and Slope*	**65811**
4	Cubic Fixed Effects	69203
	Random Intercept	66715
	Random Intercept and Slope	66047

* **Bold indicates preferred model.**

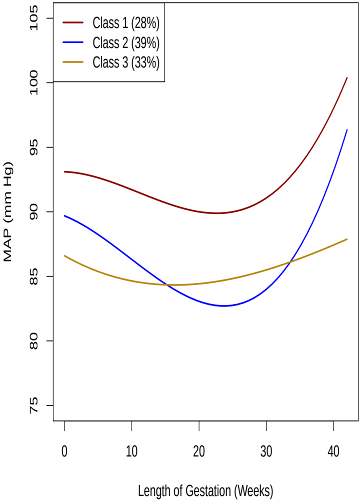
MAP Trajectories

Fig. 5: Posterior MAP trajectories.



MAP Trajectories

Fig. 5: Posterior MAP trajectories.



Class 1

	PTB		
LBW	Yes	No	
Yes	0.13	0.05	**0.18**
No	0.07	0.75	0.82
	0.20	0.80	

MAP Trajectories

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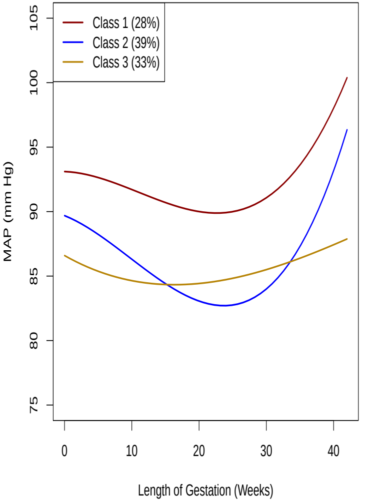

Class 1

LBW	PTB Yes	PTB No	
Yes	0.13	0.05	**0.18**
No	0.07	0.75	0.82
	0.20	0.80	

Class 2

LBW	PTB Yes	PTB No	
Yes	0.01	0.08	**0.09**
No	0.04	0.87	0.91
	0.05	0.95	

MAP Trajectories

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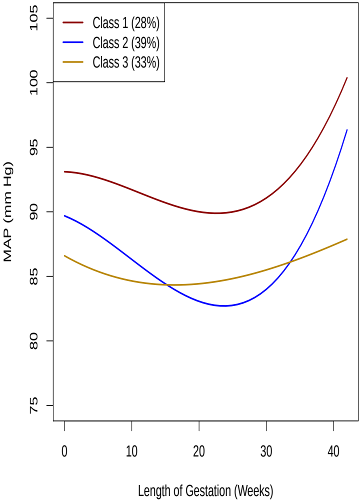

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Class 2

LBW	PTB Yes	PTB No	
Yes	0.01	0.08	**0.09**
No	0.04	0.87	0.91
	0.05	0.95	

Class 3

LBW	PTB Yes	PTB No	
Yes	0.08	0.03	**0.11**
No	0.07	0.82	0.89
	0.15	0.85	

Class-Membership Probabilities

- Can obtain class-membership probabilities as a function of covariates
- For example:
  - Reference Group: Non-Hispanic white, age 21–34 years, multiparous
  - "High-risk" Group: Non-Hispanic black, age > 34, first child

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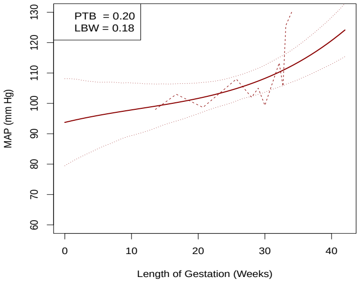
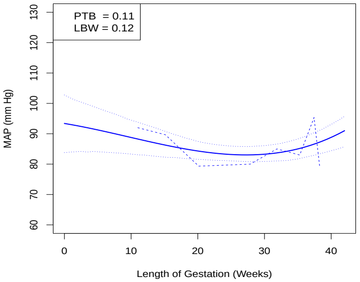
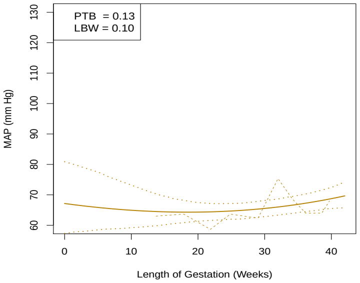
Table 3: Predicted class-membership probabilities by covariate profile.

	Class-Membership Probabilities		
Covariate Profile	Class 1	Class 2	Class 3
Reference Group	0.13	0.48	0.39
High-Risk Group	0.39	0.34	0.27

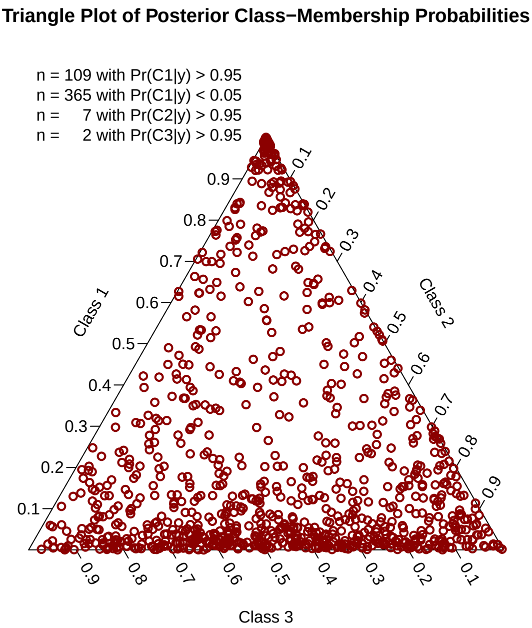
Predicted MAP Curves







Posterior Probability Plot



Recap

- Proposed a growth mixture model to jointly model three outcomes: MAP, PTB and LBW
- The model partitions women into distinct classes characterized by a mean MAP curve and joint probabilities of PTB and LBW
- Bivariate probit used to model PTB and LBW
- Patient covariates influence class-membership probabilities
- Our analysis identified three distinct MAP classes with unique risks of PTB and LBW

Future Directions

- Model could be applied to other settings with a longitudinal biomarker and correlated binary outcomes (e.g., two related diseases)
- More flexible modeling of MAP curves (e.g., via splines)
- Allow probabilities of PTB and LBW to vary by subject, not just class
    - Introduce covariates and random effects into biprobit model for PTB, LBW
- Discrete survival model for gestational length

Thanks

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