Regression Analysis of Dependent Binary Data for Estimating Disease Etiology from Case-Control Studies ("Small-Area Estimation" of Disease Etiology)

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- **Motivation for this talk**: PEFs may vary by season, a child's age, HIV status, disease severity

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- Continuous covariates: the first p_1 and q_1 elements of $\boldsymbol{X}_i$ and $\boldsymbol{W}_i$, respectively.

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Model : (to be fitted)

- $J = 7$: noisy presence/absence of 2 bacteria and 5 viruses in nasopharyngeal cavities by polymerase chain reaction (PCR)
- Causes: seven single-pathogen causes plus an “Not Specified” (NoS) cause; So $L = J + 1$
- $\boldsymbol{X}_i$: enrollment date, age ($<$ or $>$ 1 year), disease severity for cases (severe or very severe), HIV status (+/-)
- $\boldsymbol{W}_i$: $\boldsymbol{X}_i$ minus “disease severity”.

PERCH Data: Sparsely-Populated Strata

Table: The observed count (frequency) of cases and controls by age, disease severity and HIV status (1: yes; 0: no). The marginal fractions among cases and controls for each covariate are shown at the bottom. Results from the regression analyses are shown later for the first two strata.

age ≥ 1	very severe (VS) (case-only)	HIV positive	# cases (%) total: 524 (100)	# controls (%) total: 964 (100)
$\longrightarrow$ 0	0	0	208 (39.7)	545 (56.5)
$\longrightarrow$ 1	0	0	72 (13.7)	278 (28.8)
0	1	0	116 (22.1)	0
1	1	0	33 (6.3)	0
0	0	1	37 (7.1)	85 (8.8)
1	0	1	24 (4.5)	51 (5.3)
0	1	1	25 (4.8)	0
1	1	1	3 (0.6)	0
case: 25.2%	34.5%	17.0%		
control: 34.3%	-	14.1%		

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5. Example of restricted latent class models (RLCM, Xu, 2017, AOS) with one (pLCM) or more (nested pLCM) sets of response probability parameters

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Gap 1b Informative TPR priors are often elicited for a case population and rarely for each stratum; Reusing independent prior distributions of the TPRs across all the strata will lead to overly-optimistic posterior uncertainty in $\boldsymbol{\pi}^*$, hampering policy decisions.

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(b) specifies parsimonious functional dependence of $\boldsymbol{\pi}$ upon covariates such as additivity, and

(c) correctly assesses the posterior uncertainty of the PEF functions and the overall PEFs $\boldsymbol{\pi}^*$ by applying the TPR priors just once.

Quick Review: Nested Partially Latent Class Models (npLCM)

For simplicity, we assume “single-pathogen causes”

npLCM Framework (no Covariates)

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The likelihood:

$$L = L_1 \cdot L_0 = \left\{ \prod_{i:Y_i=1} \sum_{\ell=1}^{L} \pi_\ell \cdot \boldsymbol{P}_{1\ell}(\boldsymbol{M}_i; \boldsymbol{\Theta}, \boldsymbol{\Psi}, \boldsymbol{\eta}) \right\} \times \prod_{i':Y_{i'}=0} \boldsymbol{P}_0(\boldsymbol{M}_{i'}; \boldsymbol{\Psi}, \boldsymbol{\nu})$$

Special Case: pLCM (Wu et al., 2016)

Control model:

1. $\boldsymbol{P}_0(\boldsymbol{m}) = \prod_{j=1}^{J}\{\psi_j\}^{m_j}\{1-\psi_j\}^{1-m_j} = \Pi(\boldsymbol{m};\boldsymbol{\psi})$
   - 1a. $\Pi(\boldsymbol{m};\boldsymbol{s}) = \prod_{j=1}^{J}\{s_j\}^{m_{ij}}\{1-s_j\}^{1-m_{ij}}$ is the probability mass function for a product Bernoulli distribution given the success probabilities $\boldsymbol{s} = (s_1,\ldots,s_J)^\top$, $0 \leq s_j \leq 1$
   - 1b. Parameters $\boldsymbol{\psi} = (\psi_1,\ldots,\psi_J)^\top$ represent the positive rates absent disease, referred to as "false positive rates" (FPRs).

Local Independence: $M_{ij} \perp M_{ij'} \mid I = 0$

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   - 2b. on the *non-causative* pathogens $\mathbb{P}(\boldsymbol{M}_{i[-\ell]} \mid I_i = \ell, Y_i = 1, \boldsymbol{\psi}_{[-\ell]}) = \Pi(\boldsymbol{M}_{[-\ell]}; \boldsymbol{\psi}_{[-\ell]})$, where $\boldsymbol{a}_{[-\ell]}$ represents all but the ℓ-th element in a vector $\boldsymbol{a}$.

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2a-2b. Non-interference: disease-causing pathogen(s) are more frequently detected among cases than controls ($\theta_\ell > \psi_\ell$) and the non-causative pathogens are observed with the same rates among cases as in controls

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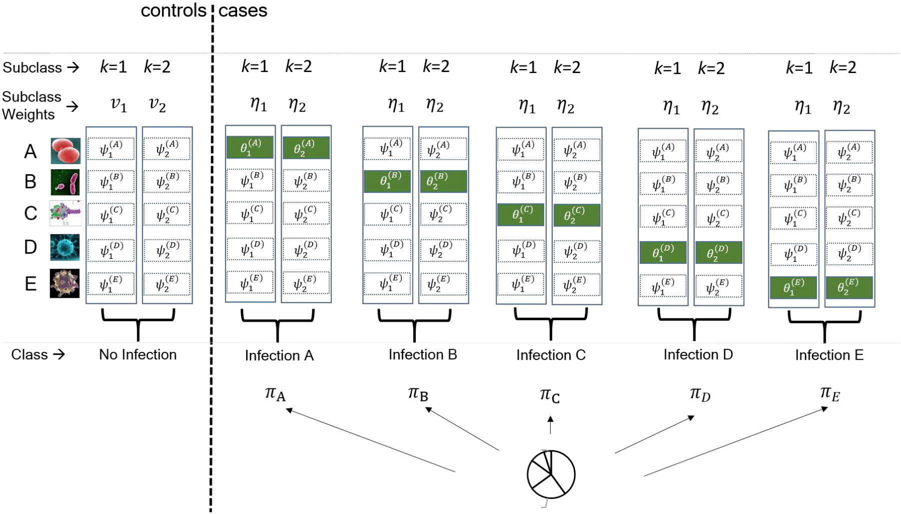
  - Simplex factor model; similar to mixed-membership model (Cf. Bhattacharya and Dunson, 2012, *JASA*)
  - PARAFAC decomposition (Cf. Dunson and Xing, 2009, *JASA*)

Nested Partially-Latent Class Models (npLCM; Wu and Zeger, 2016)

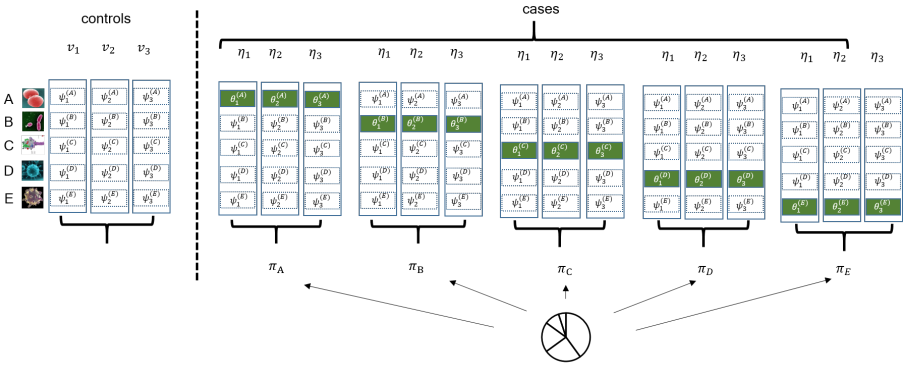
Example: 5 Pathogens, 2 Subclasses; BrS Data Only



	controls		cases									
Subclass →	k=1	k=2	k=1	k=2	k=1	k=2	k=1	k=2	k=1	k=2	k=1	k=2
Subclass Weights →	ν_1	ν_2	η_1	η_2	η_1	η_2	η_1	η_2	η_1	η_2	η_1	η_2
A	$\psi_1^{(A)}$	$\psi_2^{(A)}$	$\theta_1^{(A)}$	$\theta_2^{(A)}$	$\psi_1^{(A)}$	$\psi_2^{(A)}$	$\psi_1^{(A)}$	$\psi_2^{(A)}$	$\psi_1^{(A)}$	$\psi_2^{(A)}$	$\psi_1^{(A)}$	$\psi_2^{(A)}$
B	$\psi_1^{(B)}$	$\psi_2^{(B)}$	$\psi_1^{(B)}$	$\psi_2^{(B)}$	$\theta_1^{(B)}$	$\theta_2^{(B)}$	$\psi_1^{(B)}$	$\psi_2^{(B)}$	$\psi_1^{(B)}$	$\psi_2^{(B)}$	$\psi_1^{(B)}$	$\psi_2^{(B)}$
C	$\psi_1^{(C)}$	$\psi_2^{(C)}$	$\psi_1^{(C)}$	$\psi_2^{(C)}$	$\psi_1^{(C)}$	$\psi_2^{(C)}$	$\theta_1^{(C)}$	$\theta_2^{(C)}$	$\psi_1^{(C)}$	$\psi_2^{(C)}$	$\psi_1^{(C)}$	$\psi_2^{(C)}$
D	$\psi_1^{(D)}$	$\psi_2^{(D)}$	$\psi_1^{(D)}$	$\psi_2^{(D)}$	$\psi_1^{(D)}$	$\psi_2^{(D)}$	$\psi_1^{(D)}$	$\psi_2^{(D)}$	$\theta_1^{(D)}$	$\theta_2^{(D)}$	$\psi_1^{(D)}$	$\psi_2^{(D)}$
E	$\psi_1^{(E)}$	$\psi_2^{(E)}$	$\psi_1^{(E)}$	$\psi_2^{(E)}$	$\psi_1^{(E)}$	$\psi_2^{(E)}$	$\psi_1^{(E)}$	$\psi_2^{(E)}$	$\psi_1^{(E)}$	$\psi_2^{(E)}$	$\theta_1^{(E)}$	$\theta_2^{(E)}$
Class →	No Infection		Infection A		Infection B		Infection C		Infection D		Infection E	
			π_{A}		π_{B}		π_{C}		π_D		π_E	

Nested Partially-Latent Class Models (npLCM; Wu and Zeger, 2016)

Example: 5 Pathogens, 3 Subclasses; BrS Data Only


controls
ν_1 ν_2 ν_3
A
B
C
D
E
$\psi_1^{(A)}$ $\psi_2^{(A)}$ $\psi_3^{(A)}$
$\psi_1^{(B)}$ $\psi_2^{(B)}$ $\psi_3^{(B)}$
$\psi_1^{(C)}$ $\psi_2^{(C)}$ $\psi_3^{(C)}$
$\psi_1^{(D)}$ $\psi_2^{(D)}$ $\psi_3^{(D)}$
$\psi_1^{(E)}$ $\psi_2^{(E)}$ $\psi_3^{(E)}$
cases
η_1 η_2 η_3
$\theta_1^{(A)}$ $\theta_2^{(A)}$ $\theta_3^{(A)}$
$\theta_1^{(B)}$ $\theta_2^{(B)}$ $\theta_3^{(B)}$
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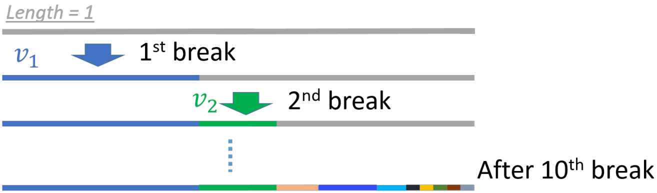
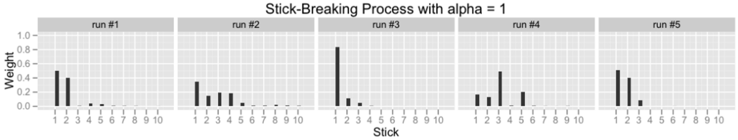
$\theta_1^{(D)}$ $\theta_2^{(D)}$ $\theta_3^{(D)}$
$\theta_1^{(E)}$ $\theta_2^{(E)}$ $\theta_3^{(E)}$
π_A
π_B
π_C
π_D
π_E

Encourage Few Subclasses: Stick-Breaking Prior

$V_j \sim \text{Beta}(1, \alpha)$; Example: $K = 10$, $\alpha = 1$





- On average, the first several segments receive most weights

npLCM: Likelihood and Prior

BrS Data Only

- Likelihood

$$
\begin{aligned}
\boldsymbol{P}_0(\boldsymbol{M}_i = \boldsymbol{m}) &= \sum_{k=1}^{K} \nu_k \prod_{j=1}^{J} \left\{\psi_k^{(j)}\right\}^{m_j} \left\{1-\psi_k^{(j)}\right\}^{1-m_j}, \\
\boldsymbol{P}_1(\boldsymbol{M}_i = \boldsymbol{m}) &= \sum_{j=1}^{J} \pi_j \sum_{k=1}^{K} \left[\eta_k \left\{\theta_k^{(j)}\right\}^{m_j} \left\{1-\theta_k^{(j)}\right\}^{1-m_j} \prod_{\ell \neq j} \left\{\psi_k^{(j)}\right\}^{m_\ell} \left\{1-\psi_k^{(j)}\right\}^{1-m_\ell}\right],
\end{aligned}
$$

- Prior:

$$
\begin{aligned}
\boldsymbol{\pi} &\sim \text{Dirichlet}(.5, \ldots, .5), \\
\psi_k^{(j)} &\sim \text{Beta}(1,1),\ \theta_k \sim \text{Beta}(c_{1kj}, c_{2kj}), j = 1, ..., J; k = 1, ..., \infty, \\
Z_{i'} \mid I_{i'}^L = j &\sim \sum_{k=1}^{\infty} U_k \prod_{\ell<k} [1-U_\ell]\, \delta_k, \quad U_k \sim \text{Beta}(1, \alpha_0),\ \text{for all cases}, \\
Z_i &\sim \sum_{k=1}^{\infty} V_k \prod_{\ell<k} [1-V_\ell] \delta_k, \quad V_k \sim \text{Beta}(1, \alpha_0),\ \text{for all controls}, \\
\alpha_0 &\sim \text{Gamma}(0.25, 0.25),
\end{aligned}
$$

Regression Extension for P_0 and P_1: letting π_ℓ, ν_k, η_k depend on covariates

Roadmap

Let three sets of parameters in an npLCM (pg.17) depend on the observed covariates

1x. Etiology regression function among cases, $\{\pi_\ell(\boldsymbol{x}), \ell \neq 0\}$, which is of primary scientific interest

2x. Conditional probability of measurements $\boldsymbol{m}$ given covariates $\boldsymbol{w}$ in controls: $\boldsymbol{P}_0(\boldsymbol{m}; \boldsymbol{w}) = [\boldsymbol{M} = \boldsymbol{m} \mid \boldsymbol{W} = \boldsymbol{w}, I = 0]$,

3x. 2x above, but in the case class ℓ:
$\boldsymbol{P}_{1\ell}(\boldsymbol{m}; \boldsymbol{w}) = [\boldsymbol{M} = \boldsymbol{m} \mid \boldsymbol{W} = \boldsymbol{w}, I = \ell]$, $\ell = 1, \ldots, L$

note Keep the specifications for the TPRs and FPRs ($\boldsymbol{\Theta}$, $\boldsymbol{\Psi}$) as in the original npLCM.

Etiology Regression $\boldsymbol{\pi}_\ell(\boldsymbol{X})$

$\pi_\ell(\boldsymbol{X})$ is the primary target of inference.

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3. Over-parameterized multinomial logistic regression: $\pi_{i\ell} = \pi_\ell(\boldsymbol{X}_i) = \exp\{\phi_\ell(\boldsymbol{X}_i)\}/\sum_{\ell'=1}^{L} \exp\{\phi_{\ell'}(\boldsymbol{X}_i)\}$, $\ell = 1, ..., L$, where $\phi_\ell(\boldsymbol{X}_i) - \phi_L(\boldsymbol{X}_i)$ is the log odds of case i in disease class ℓ relative to L: $\log \pi_{i\ell}/\pi_{iL}$.

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5a. Use B-spline basis expansion to approximate $f_{\ell j}^\pi(\cdot)$ and use P-spline for estimating smooth functions.

5b. $\widetilde{\boldsymbol{x}}$ is the subvector of the predictors $\boldsymbol{x}$; $\boldsymbol{\Gamma}_\ell^\pi = (\boldsymbol{\beta}_{\ell j}^\pi, \boldsymbol{\gamma}_\ell^\pi)$.

$\boldsymbol{P}_0$: Multivariate binary regression for controls

Desirable properties

Model Specification:

- Model space large enough for complex conditional dependence of $\boldsymbol{M}$ given covariates $\boldsymbol{W}$
- Upward compatibility, or reproducibility (invariant parameter interpretation with increasing dimensions or complex patterns of missing responses)

Estimation:

- Consistency and Efficiency
- Adaptivity: regularization to adapt to the difficulty of the problem, e.g., model residual dependence $[\boldsymbol{M} \mid \boldsymbol{W}, I = 0]$ only if necessary; model the effect of covariates only if necessary

Regression Specifications: For Controls

- The pmf for controls' measurements:
  $Pr(\boldsymbol{M}_i = \boldsymbol{m} \mid \boldsymbol{W}_i, I_i = 0) = \sum_{k=1}^{K} \nu_k(\boldsymbol{W}_i)\Pi(\boldsymbol{m}; \Psi_k)$,
  $\Psi_k = (\psi_k^{(1)}, \ldots, \psi_k^{(J)})'$

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- An equivalent generative process:

$$
\begin{aligned}
\text{sample subclass indicator}: &\quad Z_i \mid \boldsymbol{W}_i \sim \text{Categorical}_K(\boldsymbol{\nu}(\boldsymbol{W}_i))\\
\text{generate measurements}: &\quad M_{ij} \mid Z_i = k \sim \text{Bernoulli}(\psi_k^{(j)}),\\
&\quad \text{independently for } j = 1, ..., J.
\end{aligned}
$$

Regression Specifications: Covariate Dependent Weights for Controls

Stick-breaking parametrization of weight functions $\nu_k(\boldsymbol{W}_i) = P(Z_i = k \mid \boldsymbol{W}_i)$ by

$$h_k(\boldsymbol{W}_i; \boldsymbol{\Gamma}_k^{\nu}) = \begin{cases} g(\alpha_{ik}^{\nu}) \prod_{s<k} \{1 - g(\alpha_{is}^{\nu})\}, & \text{if } k < K, \\ \prod_{s<k} \{1 - g(\alpha_{is}^{\nu})\}, & \text{if } k = K, \end{cases}$$

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We specify α_{ik}^ν via additive models at g^{-1} scale ($g(\cdot) = 1/(1 + \exp\{\cdot\})$):

$$\alpha_{ik}^\nu = \mu_{k0} + \sum_{j=1}^{q_1} f_{kj}(\boldsymbol{W}_{ij}; \boldsymbol{\beta}_{kj}^\nu) + \widetilde{\boldsymbol{W}}_i^\top \gamma_k^\nu, \; k = 1, \ldots, K-1.$$

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Expanded the smooth functions by B-spline bases with coefficients $\boldsymbol{\beta}_{kj}^{\nu}$; $\widetilde{\boldsymbol{w}}$ is a subvector of covariates $\boldsymbol{w}$

Adaptivity Considerations

Proposed Model

- Prevent overfitting when the regression is easy, and improve interpretability
- We *a priori* place substantial probabilities on models with the following two features:
  a) Smooth weight regression curves $\nu_k(\cdot)$ in by Bayesian Penalized-Splines (P-Splines) combined with mixture priors on spline coefficients to sensitively distinguish constant $\alpha_k^\nu(\cdot)$ from flexible smooth curves, and,
  b) Few subclasses with effective weights (in the sense that $\nu_k(\cdot)$ is bounded away from 0 and 1) using a novel additive half-Cauchy prior for μ_{k0}.

On Consideration b) Selective Stopping, or "Uniform Shrinkage over Simplex"

Proposed Model

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Proposed Model

- We let $\mu_{k0} = \sum_{j=1}^{k} u_{kj}\mu^*_{k0}$ where $u_{kj}, 1 \le j \le k$ are pre-specified trangular array of positive values.

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- We specify the prior distributions for μ^{*}_{k0} to be heavy-tailed:

$$\mu^{*}_{k0} \sim Cauchy^{+}(0, s_k),\ k = 1, \ldots, K,$$

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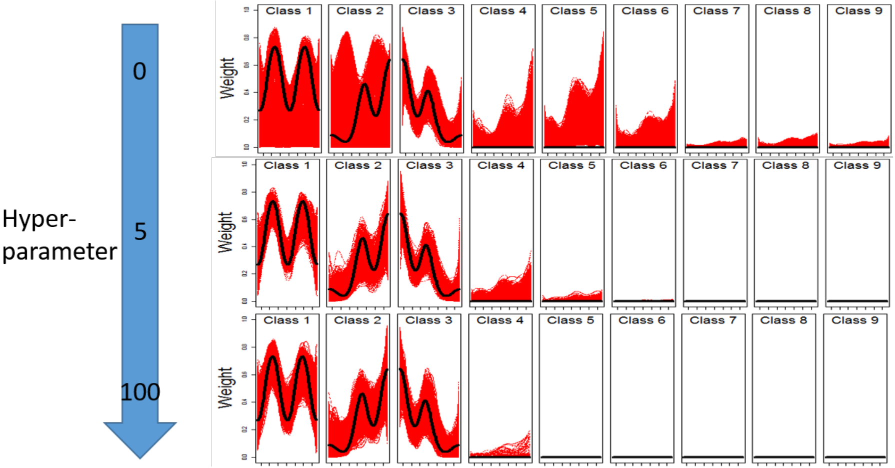
- Large values of s_k produce large μ^*_{k0} and help stop stick-breaking at class k, while small values let the stick-breaking continue to Step $k + 1$.
- Encourages using a small number of classes (K) to approximate the observed 2^J probability contingency table in finite samples.

Estimation Performance

Simulation: With Covariate



X-axis: covariate values

Y-axis: weight; 0 to 1.

Subclass Weight Regression: For Cases

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- $\boldsymbol{p}_{k\ell} = \{p_{k\ell}^{(j)}, j = 1, \ldots, J\}$ are positive rates for J measurements in subclass k of disease class ℓ:
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- $\alpha_{ik}^{\eta} = \alpha_k^{\eta}(\boldsymbol{W}_i; \boldsymbol{\Gamma}_k^{\boldsymbol{\eta}}) = \mu_{k0} + \sum_{j=1}^{q_1} f_{kj}(W_{ij}; \boldsymbol{\beta}_{kj}^{\eta}) + \widetilde{\boldsymbol{W}}_i^{\top} \boldsymbol{\gamma}_k^{\eta}$, where $\boldsymbol{\Gamma}_k^{\eta} = \{\mu_{k0}, \{\boldsymbol{\beta}_{kj}^{\eta}\}, \boldsymbol{\gamma}_k^{\eta}\}$ are the regression parameters.

Subclass Weight Regression: For Cases

The pmf for cases' measurements:

$Pr(\boldsymbol{M}_i = \boldsymbol{m}) = \sum_{\ell=1}^{L} \pi_{i\ell} \sum_{k=1}^{K} \eta_{ik} \Pi(\boldsymbol{M}_i; \boldsymbol{p}_{k\ell})$

- $\boldsymbol{p}_{k\ell} = \{p_{k\ell}^{(j)}, j = 1, \ldots, J\}$ are positive rates for J measurements in subclass k of disease class ℓ: $p_{k\ell}^{(j)} = \left\{\theta_k^{(j)}\right\}^{\mathbb{I}\{j=\ell\}} \cdot \left\{\psi_k^{(j)}\right\}^{1-\mathbb{I}\{j=\ell\}}$
- Equals the TPR $\theta_k^{(j)}$ for a causative pathogen and the FPR $\psi_k^{(j)}$ otherwise
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- we use μ_{k0} from the control regression to ensure important subclasses in the cases

npLCM Regression Framework

The npLCM regression framework is then obtained as:

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- Cases likelihood with covariates:

$$L_1^{\text{reg}} = \prod_{i:Y_i=1} \left\{ \sum_{\ell=1}^{L} \left[\pi_\ell(\boldsymbol{X}_i; \boldsymbol{\Gamma}_\ell^{\pi}) \sum_{k=1}^{K} \left\{ \boldsymbol{\eta}_{ik} \cdot \Pi(\boldsymbol{M}_i; \boldsymbol{p}_{k\ell}) \right\} \right] \right\}, \quad (2)$$

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The joint likelihood for the regression model can be written as: $L^{\text{reg}} = L_1^{\text{reg}} \times L_0^{\text{reg}}$.

Prior Specifications

Unknown parameters:

- etiology regression coefficients ($\{\mathbf{\Gamma}_\ell^\pi\}$),
- subclass mixing weight parameters for cases ($\{\mathbf{\Gamma}_k^\eta\}$) and controls ($\{\mathbf{\Gamma}_k^\nu\}$),
- true and false positive rates ($\mathbf{\Theta} = \{\theta_k^{(j)}\}, \mathbf{\Psi} = \{\psi_k^{(j)}\}$).

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To avoid potential overfitting, we *a priori* introduce:

- (a) few non-trivial subclasses via novel additive half-Cauchy prior for the intercepts $\{\mu_{k0}\}$
- (b) for continuous variable: smooth regression curves $\pi_\ell(\cdot)$, $\nu_k(\cdot)$ and $\eta_k(\cdot)$ by Bayesian Penalized-splines (Lang, 2004) combined with shrinkage priors on spline coefficients (Ni et.al, 2015) (to encourage towards constant values)

Posterior Inference

Use Markov chain Monte Carlo (MCMC) algorithm to approximate joint posterior distribution

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Fit npLCMs (w/ or w/out covariates using R package baker (`https://github.com/zhenkewu/baker`)

- calls Bayesian model fitting software JAGS 4.2.0 (Plummer et al., 2003) from within R
- provides functions to visualize the posterior distributions of the unknowns
- also performs posterior predictive model checking

Simulation Results

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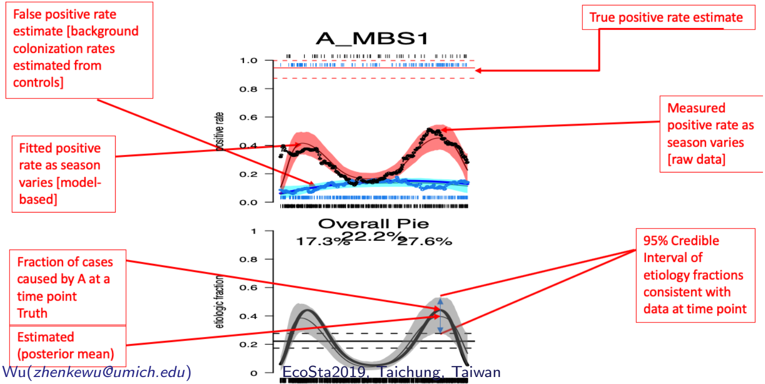
- Simulation II: determining overall PEF π_ℓ^* (empirical average) to quantify disease burdens in a population (potential policy interest)

Simulation I Results

- $N_d = 500$ cases and $N_u = 500$ controls for each of two levels of S (discrete covariate); Uniformly sample the subjects' enrollment dates over a period of 300 days.

Etiology Regression Curves: Seasonality



False positive rate estimate [background colonization rates estimated from controls]

True positive rate estimate

Fitted positive rate as season varies [model-based]

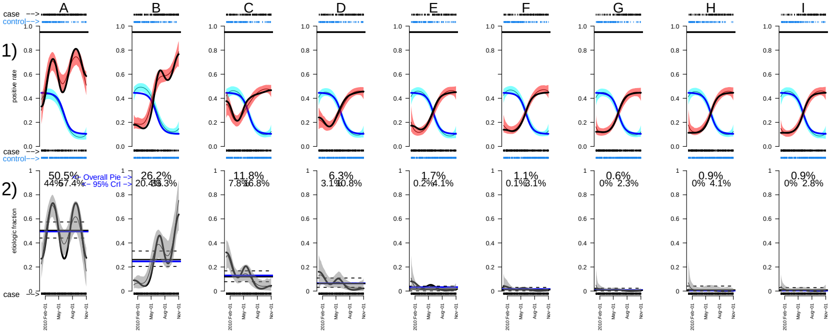
Measured positive rate as season varies [raw data]

Fraction of cases caused by A at a time point Truth

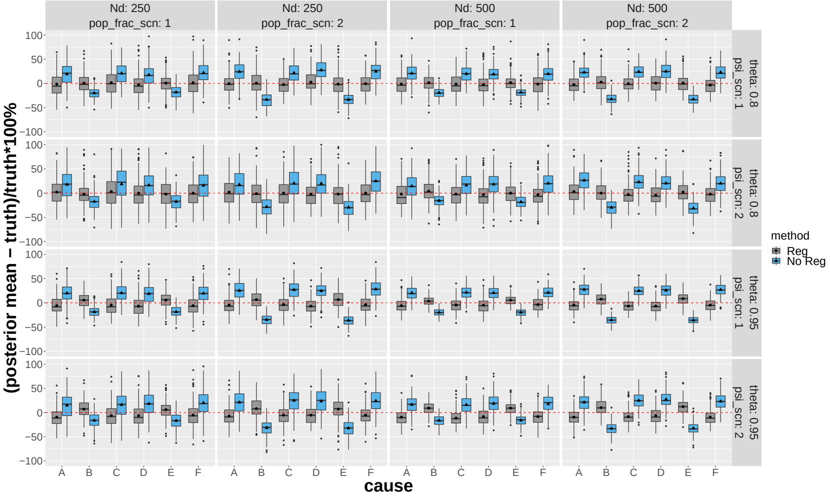
Estimated (posterior mean)

95% Credible Interval of etiology fractions consistent with data at time point

Simulation I: Recovery of Truth $\pi_\ell^0(t, S = s)$



Simulation II: Regression Model Reduces the Percent Relative Bias in Recovering the Overall PEFs π_ℓ^*



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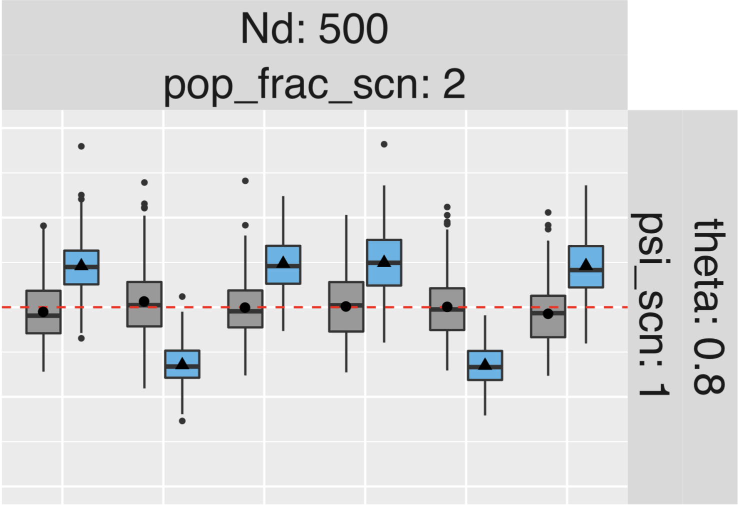
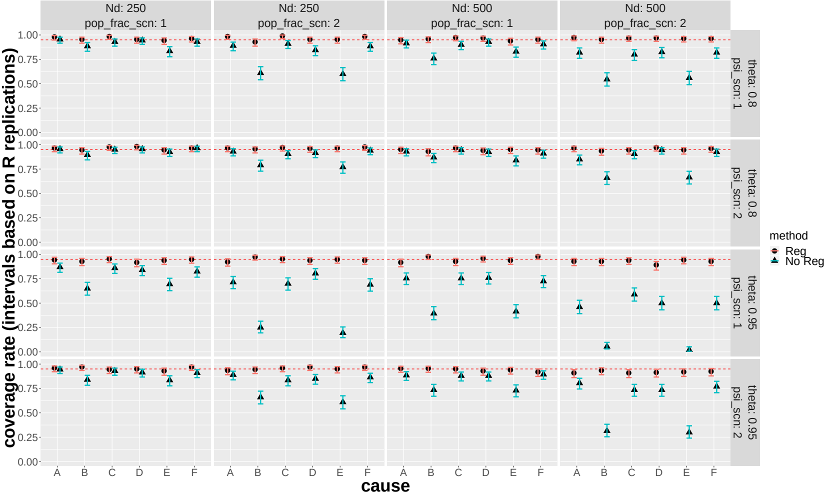


Simulation II: Regression Model Produces More Valid 95% CrIs in Recovering the Overall PEFs π_ℓ^*



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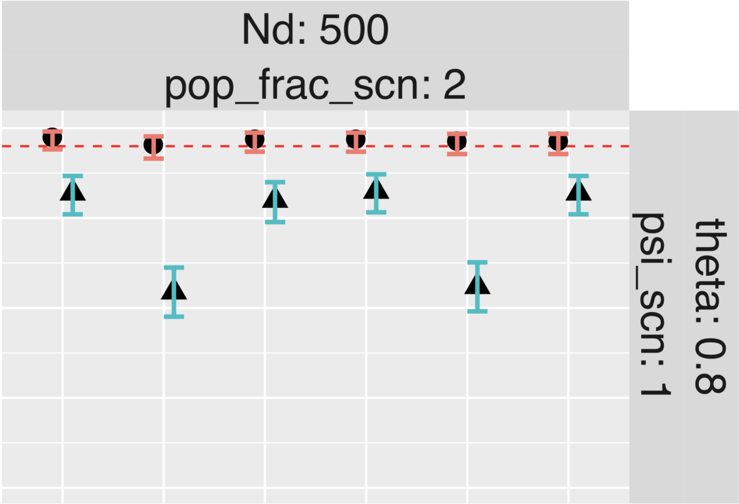

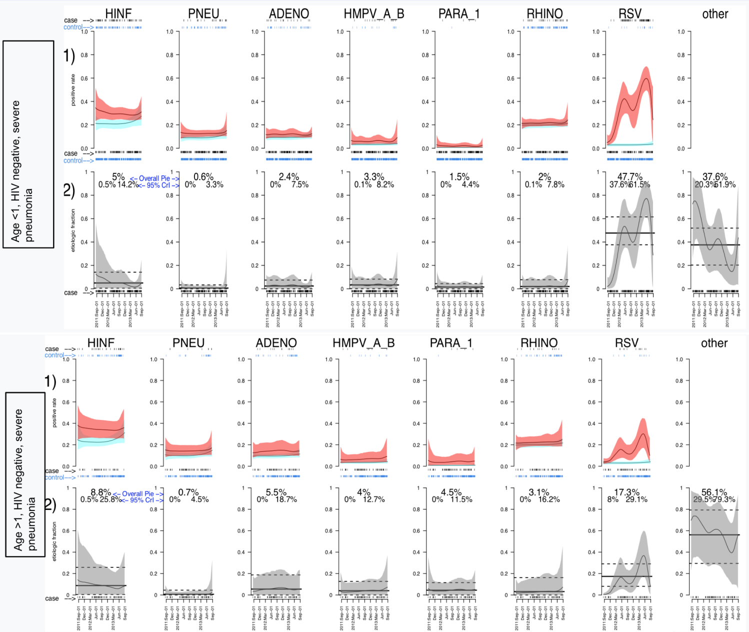
Age <1, HIV negative, severe pneumonia
1)
2)
HINF
PNEU
ADENO
HMPV_A_B
PARA_1
RHINO
RSV
other
case -->
control-->
positive rate
etiologic fraction
5%
0.5% 14.2%
<- Overall Pie ->
<- 95% CrI ->
0.6%
0% 3.3%
2.4%
0% 7.5%
3.3%
0.1% 8.2%
1.5%
0% 4.4%
2%
0.1% 7.8%
47.7%
37.6% 61.5%
37.6%
20.3% 51.9%
2011:Sep-01
Dec-01
2012:Mar-01
Jun-01
Sep-01
Dec-01
2013:Mar-01
Jun-01
Sep-01
Age >1, HIV negative, severe pneumonia
8.8%
0.5% 25.8%
0.7%
0% 4.5%
5.5%
0% 18.7%
4%
0% 12.7%
4.5%
0% 11.5%
3.1%
0% 16.2%
17.3%
8% 29.1%
56.1%
29.5% 79.3%

Discussion

Limitations: Current npLCM methods do not describe the relationship between covariates and PEFs

Contribution: We address this by including covariate regression in the framework to estimate disease etiology

Three features of our approach:

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- 2) produces covariate-dependent reference distribution for controls, which is critical for assigning cause-specific probabilities to a given case
    - because we can compare control measurements to case measurements with similar covariate values
- 3) TPR priors are only used once; avoids overly-optimistic etiology uncertainty estimates.

Future Directions

Future disease etiology studies may benefit from four improvements:

- Bayesian additive regression tree with variable selection (rather than GAM) may provide an alternative for characterizing interactions
- Class-specific predictor selection methods could be useful in the presence of many predictors in stabilizing and improving PEF estimates
- When the subset of population pathogen-cause combinations is unknown, combining the proposed method with subset selection procedures could be fruitful
- Scalable posterior inference for regression parameters will likely improve computational speed when number of disease classes/covariates is larger

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Laura Hammitt

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Some References (More at: zhenkewu.com)

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Biostatistics. 18 (2): 200-213.

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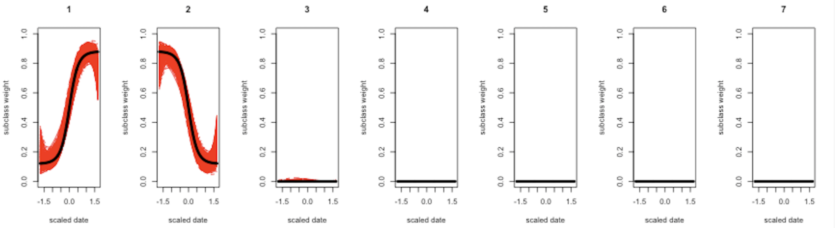
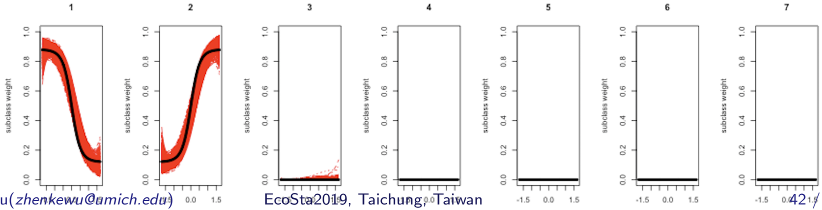
Partially Latent Class Models (pLCM) for Case-Control Studies of Childhood Pneumonia Etiology.
Journal of the Royal Statistical Society: Series C (Applied Statistics). 65:97-114.

Simulation I: Recovery of $\nu_k(t)$ and $\eta_k(t)$

True $K^0 = 2$; Model fitted using a working number $K = 7$



(a) case



Appendix: Simulation II Setup

- npLCM regression analysis with $K^* = 3$, $R = 200$ replication data sets simulated under 48 different scenarios
- $L = J = 3, 6, 9$ causes, under single-pathogen-cause assumption, BrS measurements made on N_d cases and N_u controls for each level of X where $N_d = N_u = 250$ or 500.
- $\phi_\ell(X) = \beta_{0\ell} + \beta_{1\ell}\,\mathbb{I}\{X = 2\}$ take two sets of values to reflect PEF variability across X: i) $\boldsymbol{\beta}_0^{\text{i}} = (0, 0, 0, 0, 0, 0)$, $\boldsymbol{\beta}_1^{\text{i}} = (-1.5, 0, -1.5, -1.5, 0, -1.5)$; ii) $\boldsymbol{\beta}_0^{\text{ii}} = (1, 0, 1, 1, 0, 1)$ and $\boldsymbol{\beta}_1^{\text{ii}} = (-1.5, 1, -1.5, -1.5, 1, -1.5)$
- TPRs $\theta_k^{(j)} = 0.95$ or 0.8 and FPRs $(\psi_1^{(j)}, \psi_2^{(j)}) \in \{(0.5, 0.05), (0.5, 0.15)\}$, for $j = 1, \ldots, J$.
- $\nu_k(W) = \eta_k(W) = logit^{-1}\left(\gamma_{k0} + \gamma_{k1}\,\mathbb{I}\{W = 2\}\right)$ where $(\gamma_{10}, \gamma_{11}) = (-0.5, 1.5)$ and $(\gamma_{20}, \gamma_{21}) = (1, -1.5)$.

Appendix

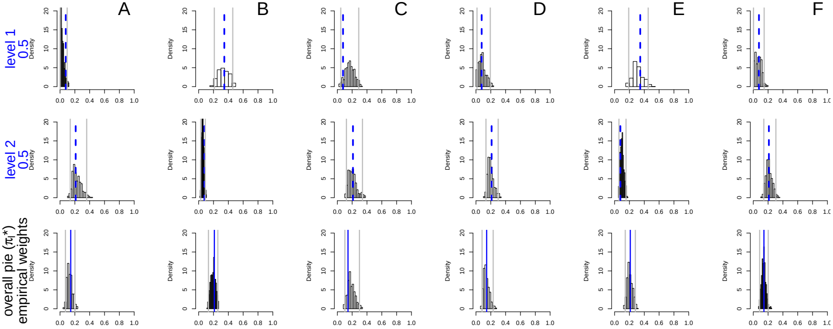


Figure: Posterior distributions of the stratum-specific (Row 1 and 2) and the overall (Bottom Row) PEFs based on a simulation with a two-level discrete covariate and $L = J = 6$ causes. The vertical gray lines indicate the 2.5% and 97.5% posterior quantiles, respectively; The truths are indicated by vertical blue dashed lines. *Row 1-2*) PEFs by stratum (level = 1,2) and cause (A-F); *Bottom*) π^*_ℓ: overall population etiologic fraction for cause A-F (empirical average of the two PEFs above).

Appendix

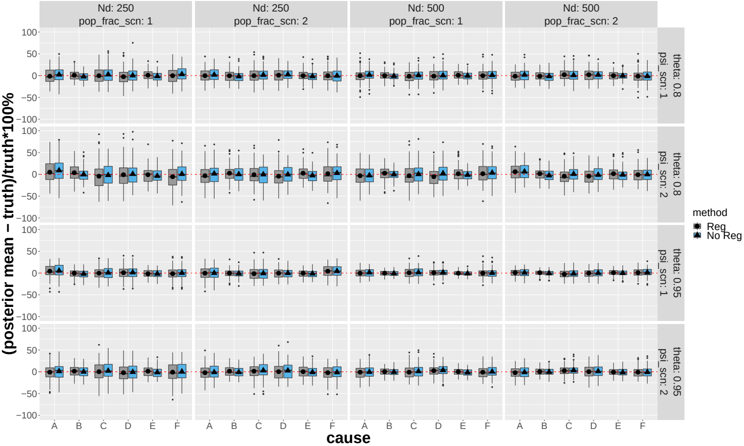
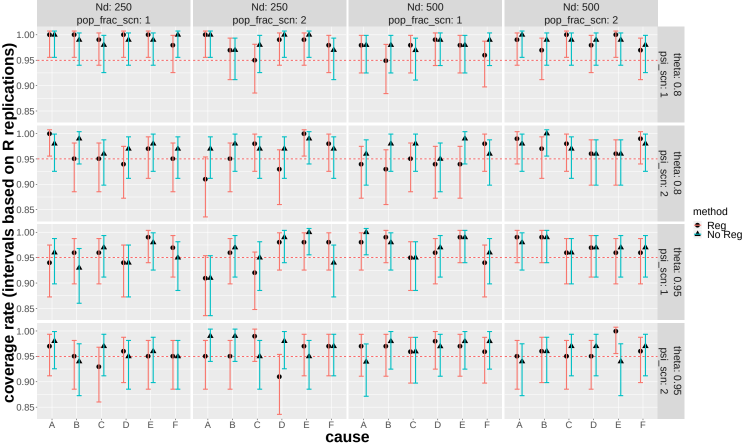


Figure: NPLCM analyses with or without regression perform similarly in terms of percent relative bias (top) and empirical coverage rates (bottom) over $R = 100$ replications in simulations where the case and control subclass weights *do not* vary by covariates. Each panel corresponds to one of 16 combinations of true parameter values and sample sizes.

Appendix



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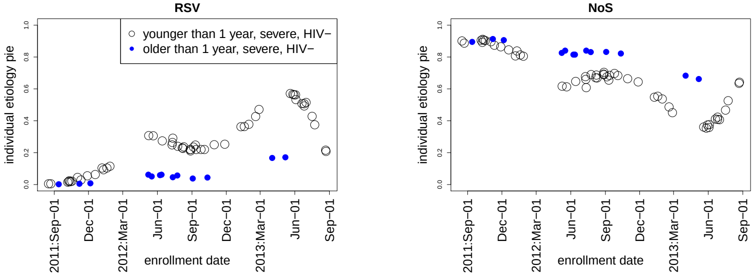

(a) Cause: RSV

(b) Cause: NoS

Figure: Individual etiology fraction estimates for RSV (left) and NoS (right) differ by age and season among HIV negative and severe pneumonia cases for whom the seven pathogens were *all tested negative* in the nasopharyngeal specimens.