Outline

1. Introduction
2. DDP Binomial mixture model
3. Simulated data examples
4. Data illustrations
5. Extensions/current work
Introduction

1. Introduction

Dose-Response Studies

- A number of subjects are exposed to several dose levels of a substance
- Results in single count at each dose level, either a collection of binary or multicategory counts

Developmental Toxicity Studies

- A number of pregnant laboratory animals (dams) are exposed to a toxin
- Recorded from each animal are the number of resorptions and/or prenatal deaths, the number of live pups, and the number of live malformed pups; may also include body weight and length of the live pups
Introduction

• Birth defects induced by toxic chemicals are investigated through developmental toxicity studies

• Key objective is to examine the relationship between the level of exposure to the toxin (dose level) and the probability of malformation (in general, response)

• Dose-response curve is defined by the probability of an outcome across the dose levels

• Quantitative risk assessment evaluates the probability that adverse effects may occur as a result of the exposure to the substance
Introduction

• Data structure for Segment II designs (exposure after implantation)
  – data at dose levels, \( x_i, i = 1, \ldots, N \), including a control group (dose = 0)
  – \( n_i \) dams at dose level \( x_i \)
  – for the \( j \)-th dam at dose \( x_i \):
    * \( m_{ij} \): number of implants
    * \( R_{ij} \): number of resorptions and prenatal deaths (\( R_{ij} \leq m_{ij} \))
    * \( y'_{ij} \): number of live pups with a malformation (\( y'_{ij} \leq m_{ij} - R_{ij} \))
  – in general, the outcomes \( \{(m_{ij}, R_{ij}, y'_{ij}) : i = 1, \ldots, N, j = 1, \ldots, n_i \} \)

  – focus on simpler form \( \{(m_{ij}, y_{ij}) : i = 1, \ldots, N, j = 1, \ldots, n_i \} \), where \( y_{ij} = R_{ij} + y'_{ij} \) is the number of combined negative outcomes

• Modeling approach can be extended for: trinomial outcomes; clustered discrete-continuous responses; studies with pre-implantation exposure
Introduction

2,4,5-T data (left) and DEHP data (right): each circle is for a particular dam, the size of the circle is proportional to the number of implants, and the coordinates of the circle are the dose level and the proportion of combined negative outcomes.
Introduction

- Several approaches based on parametric response distributions and/or customary parametric forms for dose-response curves
  - standard parametric models (e.g., Binomial or Beta-Binomial models) typically not sufficiently flexible to capture the inherent heterogeneity in the data

- Classical semiparametric or likelihood estimation for the joint distribution of the vector of binary responses associated with each dam under the assumption of exchangeability
  - more general modeling for the response distribution than traditional parametric approaches
  - however, dose-response relationships are still introduced through parametric forms – inferential challenges regarding interpolation at unobserved dose levels and for uncertainty quantification
Introduction

- Relatively limited amount of work involving Bayesian methods for developmental toxicity studies
  
  - parametric Bayesian hierarchical models for toxicology data, comprising joint discrete-continuous outcomes (Dunson et al., 2003; Faes et al., 2006)
  
  - Bayesian semiparametric model based on a product of mixtures of Dirichlet process prior structure (Dominici & Parmigiani, 2001)
Introduction

- How about a fully nonparametric Bayesian modeling approach?

- Objectives:
  - overcome limitations of parametric approaches, retaining a fully inferential probabilistic model setting
  - develop a modeling framework that provides flexibility in both the response distribution and the dose-response relationship
  - seek modeling for response distributions that are related across dose levels with the level of dependence driven by the distance between the dose level values

- Nonparametric mixture modeling using dependent Dirichlet process (DDP) priors ...
2. DDP Binomial mixture model

- Number of implants, $m$, is a random variable
- As the toxin is administered after implantation, $m$ contains no information about the dose-response relationship
  - $f(m) \equiv f(m; \lambda) = \text{Pois}(m; \lambda)$, $m \geq 1$
  - more general models can be employed

- $f(m, y) = f(m)f(y \mid m)$
- **Objective**: flexible NPB model for the dose-dependent conditional response distributions $f(y \mid m)$
• Standard parametric continuous mixture models:
  – Beta-Binomial model:
    $$y \mid m, \pi \sim \text{Bin}(y; m, \pi), \quad \pi \sim \text{Beta}(\pi; \alpha, \beta)$$
  
  – Binomial-logistic-normal model:
    $$y \mid m, \theta \sim \text{Bin} \left( y; m, \frac{e^\theta}{1+e^\theta} \right), \quad \theta \sim \text{N}(\theta; \mu, \tau^2)$$
  
  – under both formulations, dose-response curve is built parametrically through the mean of the continuous mixing distribution
DDP Binomial mixture model

- Nonparametric Binomial mixture, using a **Dirichlet process** (DP) prior for the random mixing distribution

- Constructive definition for the DP($\alpha, G_0$) prior:

\[
G(\cdot) = \sum_{l=1}^{\infty} \omega_l \delta_{\eta_l}(\cdot)
\]

  - locations $\eta_l$ i.i.d. from the centering distribution $G_0$
  - weights generated through *stick-breaking*: $\omega_1 = z_1$, $\omega_l = z_l \prod_{r=1}^{l-1} (1 - z_r)$ for $r \geq 2$, with $z_l$ i.i.d. Beta(1,$\alpha$) (independently of the $\eta_l$)

- DP mixture model

\[
f(y; G) = \int k(y; \theta) dG(\theta), \quad G \sim \text{DP}(\alpha, G_0)
\]

  for a parametric kernel distribution with density/p.m.f. $k(y; \theta)$
DDP Binomial mixture model

\[ z_1 (1 - z_1) \]

\[ (1 - z_2)(1 - z_1) \]

\[ z_3(1 - z_2)(1 - z_1) \]

\[ (1 - z_3)(1 - z_2)(1 - z_1) \]
DDP Binomial mixture model

DP mixture of Binomial distributions at a single dose level $x_1$:

$$f(y | m) \equiv f(y | m; G_{x_1}) = \int \text{Bin} \left( y; m, \frac{e^\theta}{1 + e^\theta} \right) dG_{x_1}(\theta)$$

$$G_{x_1} \sim \text{DP}(\alpha, G_{0x_1} = N(\beta_0 + \beta_1 x_1, \sigma^2))$$
DDP Binomial mixture model

two dose levels $x = (x_1, x_2)$:

$$f(y_1, y_2 \mid m_1, m_2; G_x) = \int \prod_{i=1}^2 \text{Bin} \left( y_i; m_i, \frac{e^{\theta_i}}{1 + e^{\theta_i}} \right) dG_x(\theta_1, \theta_2)$$

$$G_x \sim \text{DP}(\alpha, G_{0x} = \mathcal{N}_2((\beta_0 + \beta_1 x_1, \beta_0 + \beta_1 x_2)^T, \Sigma))$$
DDP Binomial mixture model

for any finite number of dose levels \( \mathbf{x} = (x_1, ..., x_k) \):

\[
f(y | \mathbf{m}; G_x) = \int \prod_{i=1}^{k} \text{Bin} \left( y_i; m_i, \frac{e^{\theta_i}}{1+e^{\theta_i}} \right) dG_x(\theta)
\]

\[
G_x \sim \text{DP}(\alpha, G_{0x} = \mathcal{N}_k((\beta_0 + \beta_1 x_1, ..., \beta_0 + \beta_1 x_k)^T, \Sigma))
\]

with covariance structure for \( \Sigma \) that depends on the pairwise distances between the dose levels
DDP Binomial mixture model

- Mixture probability model can be extended to the uncountable set of index points (dose levels) through a DDP prior for the collection of mixing distributions \( \{G_x : x \in X\} \), where \( X \subseteq \mathbb{R}^+ \)

- The (almost sure) discrete representation for the regular DP is extended to

\[
G_X(\cdot) = \sum_{l=1}^{\infty} \omega_l \delta_{\eta_l X}(\cdot)
\]

with the \( \eta_l X = \{\eta_l(x) : x \in X\} \) i.i.d. from a stochastic process \( G_0X \) over \( X \)
- finite dimensional versions discussed in previous slides are obtained when \( G_0X \) is a Gaussian process (GP)
- key feature of the DDP prior structure: for any finite collection of dose levels \( (x_1, ..., x_k) \) it induces a multivariate DP prior for the corresponding collection of mixing distributions \( (G_{x_1}, ..., G_{x_k}) \)
- “single-\( p \)” DDP prior (MacEachern, 2000; DeIorio et al., 2004; Gelfand et al., 2005; Rodriguez & ter Horst, 2008; Kottas & Krnjajić, 2009)
DDP Binomial mixture model

- DDP mixture of Binomial distributions:
  \[ f(y \mid m) \equiv f(y \mid m; G_X) = \int \text{Bin} \left( y; m, \frac{\exp(\theta)}{1+\exp(\theta)} \right) dG_X(\theta) \]
  \[ G_X \sim \text{DDP}(\alpha, G_{0X}) \]

- GP for \( G_{0X} \) with a linear mean function, \( E(\eta_l(x) \mid \beta_0, \beta_1) = \beta_0 + \beta_1 x \)
- constant variance, \( \text{Var}(\eta_l(x) \mid \sigma^2) = \sigma^2 \)
- isotropic power exponential correlation function,
  \[ \text{Corr}(\eta_l(x), \eta_l(x') \mid \phi) = \exp(-\phi|x - x'|^d), \]
  with \( \phi > 0 \) and (fixed) \( d \in [1, 2] \)
- hyperpriors for \( \alpha \) and \( \psi = (\beta_0, \beta_1, \sigma^2, \phi) \)

- linear mean function enables connections with parametric dose-response models, which arise as limiting cases of the DDP mixture model
DDP Binomial mixture model

- **Posterior simulation** through blocked Gibbs sampling

- Finite truncation approximation to $G_{\mathcal{X}}$:

$$G_{\mathcal{X}}^L = \sum_{l=1}^{L} p_l \delta_{Z_l \mathcal{X}}$$

  - $Z_l \mathcal{X} = \{Z_l(x) : x \in \mathcal{X}\}$, given $\psi$, are i.i.d. realizations from $G_{0\mathcal{X}}$
  - the weights $p_l$ arise from a truncated version of the stick-breaking construction: $p_1 = V_1$, $p_l = V_l \prod_{r=1}^{l-1} (1 - V_r)$, $l = 2, \ldots, L - 1$, and $p_L = 1 - \sum_{l=1}^{L-1} p_l$, with the $V_l$, given $\alpha$, i.i.d. from Beta(1, $\alpha$)

- Posterior predictive inference over observed and new dose levels, using the posterior samples from the model
Key aspects of the DDP mixture model with regard to inference:

- flexible inference at each observed dose level through a nonparametric Binomial mixture (overdispersion, skewness, multimodality ...)
- prediction at unobserved dose levels (within and outside the range of observed doses)
- level of dependence between $G_x$ and $G_{x'}$, and thus between $f(y \mid m; G_x)$ and $f(y \mid m; G_{x'})$, is driven by the distance between $x$ and $x'$ — in prediction for $f(y \mid m; G_x)$, we learn more from dose levels $x'$ nearby $x$ than from more distant dose levels
- inference for the dose-response relationship is induced by flexible modeling for underlying response distributions
DDP Binomial mixture model

- Dose-response curve?
- Alternative model formulation
  - vector of binary responses $y^* = (y_1^*, \ldots, y_m^*)$ for a generic dam with number of implants $m$ at dose level $x$
  - DDP mixture with a product Bernoulli kernel:

\[
    f^*(y^* \mid m; G_X) = \int \prod_{k=1}^m \text{Bern} \left( y_k^* ; \frac{\exp(\theta)}{1 + \exp(\theta)} \right) \, dG_X(\theta)
\]

where the same DDP prior as before would be assigned to $G_X$
- equivalent to the DDP Binomial mixture: distribution of the combined negative outcomes within a dam under the DDP Binomial mixture the same with the distribution for the sum of binary responses under the model above
DDP Binomial mixture model

- Using the mixture model formulation for the underlying binary outcomes, define the dose-response curve as the probability of a negative outcome for a generic implant expressed as a function of dose level

\[
Pr(y^* = 1; G^L_x) = \int \frac{\exp(\theta)}{1 + \exp(\theta)} \, dG^L_x(\theta) = \sum_{l=1}^{L} p_l \frac{\exp(Z_l x)}{1 + \exp(Z_l x)}
\]

- If \( \beta_1 > 0 \), the prior expectation \( E(Pr(y^* = 1; G^L_x)) \) is non-decreasing with \( x \), but prior (and thus posterior) realizations for the dose-response curve are not structurally restricted to be non-decreasing (we argue this is an asset!)

- Can also infer about intracluster correlations \( \text{Corr}(y^*_k, y^*_k'; G^L_x) \), which can change with dose \( x \)

- Risk assessment: e.g., estimation of the dose level \( x_q \) that corresponds to a specified probability, \( q \), of a negative outcome, i.e., \( q = Pr(y^* = 1; G^L_{x_q}) \)
3. Simulated data examples

- Simulated data sets generated under two distinct settings (in both cases, the values for the dose levels, number of dams, and implant vectors are taken from the 2,4,5-T data)

1. Binomial response distribution with a non-standard nonlinear function for the dose-response curve: \( \frac{\exp(h(x))}{1 + \exp(h(x))} \), where 
   \[
   h(x) = -2 + 0.04x - 0.25 \sin(2.7x) - 1.1/(1 + x^2)
   \]

2. Mixture of three Binomial-logit distributions, 
   \[
   \sum_{i=1}^{3} p_i \text{Bin}(y; m, \exp(q_i(x)))/\{1 + \exp(q_i(x))\}, \text{ where } (p_1, p_2, p_3) = (0.1, 0.4, 0.5), q_1(x) = -2 + 0.02x, q_2(x) = -10 + 0.20x, \text{ and } q_3(x) = -4 + 0.15x
   \]
Simulated data examples

Data from the first and second simulation settings (left and right panels). In each panel, the solid line denotes the true dose-response curve.
Simulated data examples

- Comparison of the DDP Binomial mixture model with a GP Binomial regression model and also with the semiparametric product of mixtures of Dirichlet process (PMDP) model (Dominici & Parmigiani, 2001)

- GP Binomial regression model: Binomial response distributions with a GP prior for the dose-response curve on the logistic scale – limiting case of the DDP mixture model (as $\alpha \to 0^+$)

- PMDP model: for $j = 1, \ldots, n_i$, $i = 1, \ldots, N$

\[
y_{ij} | F_{ij} \overset{\text{iid.}}{\sim} F_{ij}, \quad j = 1, \ldots, n_i, \quad i = 1, \ldots, N
\]

\[
F_{ij} | A_i, (\eta_0, \eta_1) \overset{\text{iid.}}{\sim} \text{DP} \left( A_i, \text{Bin} \left( m_{ij}, \frac{\exp(\eta_0 + \eta_1 x_i)}{1 + \exp(\eta_0 + \eta_1 x_i)} \right) \right)
\]
Simulated data examples

Case 1. Posterior mean (denoted by “o”) and 90% error bands (red) for $f(y \mid m = 12; G_x)$, at three dose levels, using the GP, PMDP and DDP models (left, middle and right columns). The values of the true probability mass function are denoted by “x”.

![Graphs showing simulated data examples](image-url)
Simulated data examples

Case 2. Posterior mean (denoted by “o”) and 90% error bands (red) for $f(y \mid m = 12; G_x)$, at three dose levels, using the GP, PMDP and DDP models (left, middle and right columns). The values of the true probability mass function are denoted by “x”.
4. Data illustrations

- 2,4,5-T data: data set from a developmental toxicity study regarding the effects of 2,4,5-trichlorophenoxyacetic (2,4,5-T) acid (Holson et al., 1991)
- \( N = 6 \) doses, one control and 5 active dose levels
- data suggest varying departures from the Binomial model across the dose levels
Data illustrations

2,4,5-T data
Data illustrations

2,4,5-T data. For the 6 observed doses and 2 new doses, posterior mean estimates (denoted by “o”) and 90% error bands (red) for $f(y \mid m = 12; G_x)$. 

Bayesian Nonparametric Modeling for Developmental Toxicity Studies
2,4,5-T data. Posterior densities for the intracluster correlations at each of the six observed dose levels.
2,4,5-T data. Posterior densities for the calibrated dose level corresponding to four probability thresholds.
2,4,5-T data. Posterior mean estimate and 90% error bands for the dose-response curve under the Binomial-logistic model (left), the Beta-Binomial model (middle), and the DDP Binomial mixture model (right).
Data illustrations

- DEHP data: data from an experiment that explored the effects of diethylhexalpthalate (DEHP) (TyI et al., 1983)
- number of dams per dose level is about a third of those found in the 2,4,5-T data
- drop in the proportions of combined negative outcomes from dose 0 to 25 mg/kg $\times 1000$, which may indicate a hormetic dose-response relationship
Data illustrations

DEHP data. Data (left) and posterior mean estimate and 90% error bands for the dose-response curve (right).
5. Extensions/current work

- General modeling framework for replicated count responses in dose-response settings – emphasis on data from developmental toxicity studies

- A couple of practically important extensions currently under study

- Extension for multiclassification responses:

\[ f(R, y' \mid m; G_X) = \int \text{Bin} \left( R; m, \frac{\exp(\gamma)}{1 + \exp(\gamma)} \right) \text{Bin} \left( y'; m - R, \frac{\exp(\theta)}{1 + \exp(\theta)} \right) dG_X(\gamma, \theta) \]

with \( G_X \sim \text{DDP}(\alpha, G_0X) \)
Extensions/current work

- Further extension to fully nonparametric modeling for clustered discrete-continuous outcomes
  - dam with $m$ implants at dose $x$ resulting in $R$ prenatal deaths, and vectors of binary malformation outcomes $y^* = \{y_k^*: k = 1, ..., m - R\}$ and continuous responses $u^* = \{u_k^*: k = 1, ..., m - R\}$ for all live pups
  - DDP mixture model:

$\begin{align*}
  f(R, y^*, u^* \mid m; G_X) &= \int \text{Bin} \left( R; m, \frac{\exp(\gamma)}{1 + \exp(\gamma)} \right) \prod_{k=1}^{m-R} \text{Bern} \left( y_k^*; \frac{\exp(\theta)}{1 + \exp(\theta)} \right) \\
  &\times \prod_{k=1}^{m-R} \text{N} (u_k^*; \mu, V) \, dG_X (\gamma, \theta, \mu)
\end{align*}$

again, with an extended DDP($\alpha, G_0X$) prior for $G_X$

- Different data structures: developmental toxicity studies with pre-implantation exposure
• Reference:

• UCSC Dept of Applied Math and Statistics website: www.ams.ucsc.edu

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