Nonparametric Bayesian Statistics

Debdeep Pati
Florida State University

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Incorporating constraints in NP Bayes

- Interest in relationship between a predictor x and response y adjusting for covariates z.
- In epidemiology & toxicology studies, $x =$ dose of a potentially adverse exposure
- Biologically reasonable to assume that response distribution is stochastically non-decreasing with x for any fixed z

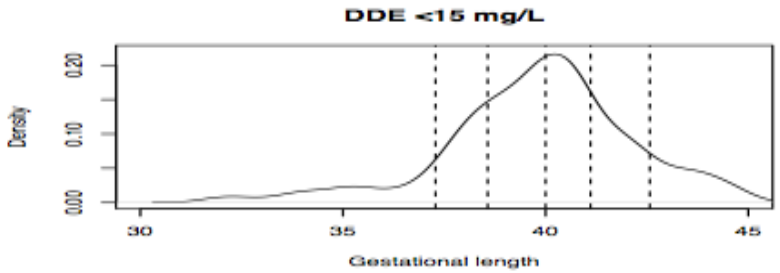
Isotonic Regression

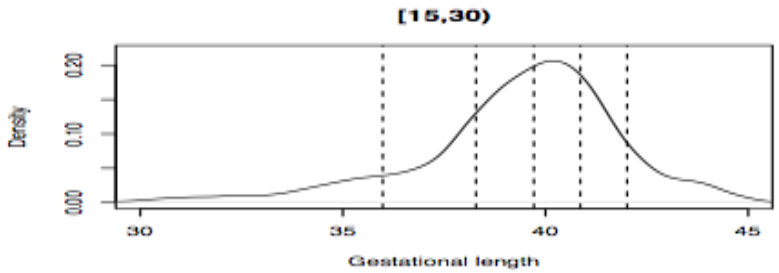
- In order to incorporate non-decreasing constraint, one may consider an isotonic regression model
- Ramsay (1988) propose monotone regression splines - flexible estimation of smoothly increasing regression curve
- In toxicology & epidemiology, interest in inferences on flat vs increasing regions - flat corresponds to no effect of predictor

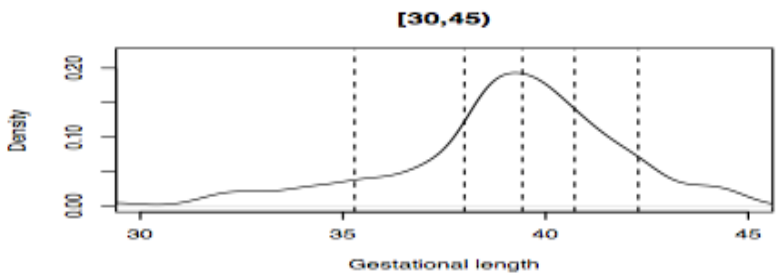
Isotonic Mean Regression $\rightarrow$ density regression

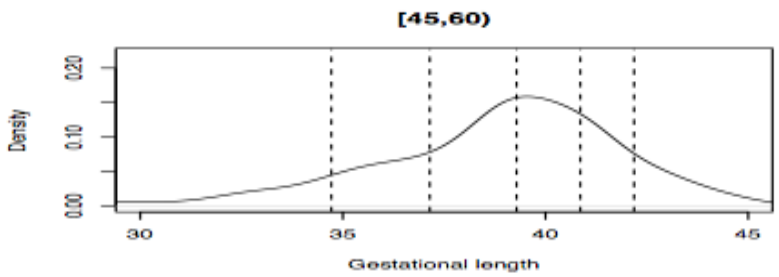
- Above methods focus on estimation of a non-decreasing function, $f(x)$, subject to $f(x) \leq f(x')$, for all $x < x'$.
- Typically, $f(x) =$ mean regression function, with residual distribution constant with x
- Casady & Cryer (1976) - isotonic quantile estimator
- Our focus: allow conditional distribution, $f(y|x)$, to change flexibly with x subject to non-increasing stochastic order

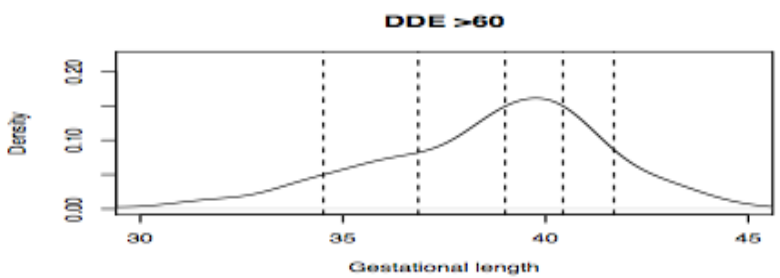
Application - DDE & Preterm Birth











Application - DDE & Preterm Birth

- Interest - how distribution of a continuous health response changes with a discrete / continuous predictor
- y_i = gestational age at delivery, x_i =level of DDE in maternal serum, z_i =potential confounders
- As exposure increases, distribution of gestational age at delivery stochastic non-increasing
- How to nonparametrically model such changes and conduct hypothesis tests

Modeling of Stochastic Ordering

- Initially consider case with two unknown distributions, P_1 and P_2 defined on $\mathcal{X}$ with $P_1 \precsim P_2$.
- Bayesian estimation considered by Gelfand & Kottas (01) - used products of independent DP components
- Our Goals:
  1. Flexible Prior on set C_E of stochastically ordered distributions
  2. Efficient MCMC approach for computation
  3. Methods for hypothesis testing

Hoff (2003, Biometrika) Formulation

- Goal is to choose a prior for $(P_1, \ldots, P_K) \in C_E$
- C_E = weakly closed convex set with extreme points $\{(\delta_s) : s = (s_1, \ldots, s_K) \in S_K\}$
- $S_K = \{(s_1, \ldots, s_K) \in \mathcal{X}^K : s_i \leq s_j \forall (i,j) \in E\}$, with E pre-specified matrix defining ordering
- Main Result: DP prior on S_K induces prior on C_E

Restricted Dependent DP (Dunson & Peddada, 07)

- Hoff (03) does not allow continuous distributions, computation is difficult & no allowance for hypothesis testing
- Applying Sethuraman (94) & Hoff (03), we define restricted dependent DP (rDDP) priors for $(P_1, \ldots, P_K) \in C_E$:

$$P_k(\cdot) = \sum_{h=1}^{\infty} \pi_h \delta_{\Theta_{hk}}, \quad \boldsymbol{\Theta}_h = (\Theta_{h1}, \ldots, \Theta_{hK}) \sim Q_0$$

  with Q_0 a base measure on S_K & $\{\pi_h\}$ = typical DP weights
- rDDP modifies DDP (MacEachern, 99) to use restricted Q_0

Two Group Example

- $(P_1, P_2) \sim rDDP(\alpha Q_0)$ implies:

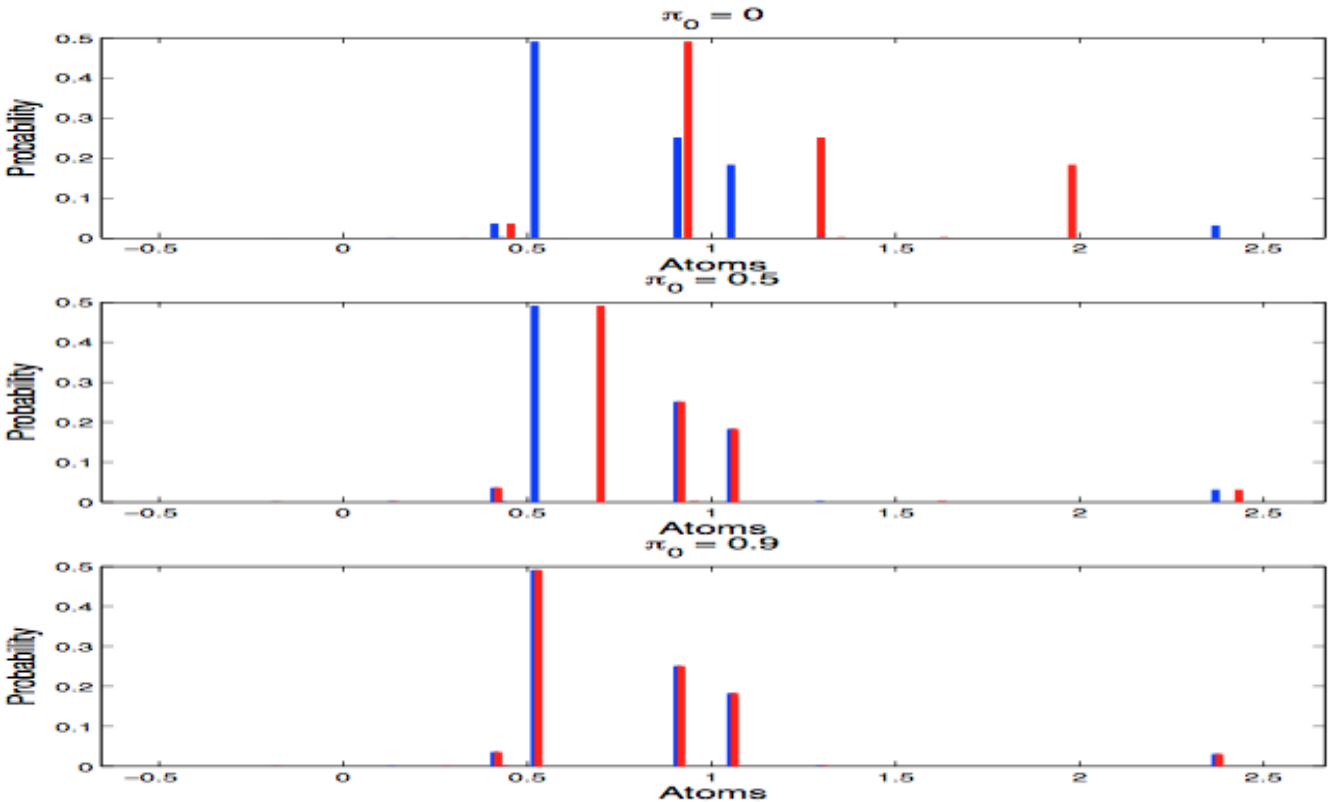
$$P_1 = \sum_{h=1}^{\infty} \pi_h \delta_{\Theta_{h1}}, \quad P_2 = \sum_{h=1}^{\infty} \pi_h \delta_{\Theta_{h2}}$$

- $(\Theta_{h1}, \Theta_{h2}) \sim Q_0$, with $Q_0(\Theta_{h1} \leq \Theta_{h2}) = 1$
- For example, $Q_0 =$ truncated bivariate normal
- To limit bias & facilitate testing, allow probability mass on the boundary by choosing Q_0 to correspond to:

$$f(\Theta_1, \Theta_2) = f_1(\Theta_1)\{\pi_0 \delta_0(\Theta_2 - \Theta_1) + (1 - \pi_0) f_2(\Theta_2 - \Theta_1).$$

where f_1 a density on $\mathbb{R}$ and f_2 is a density supported on $\mathbb{R}^+$

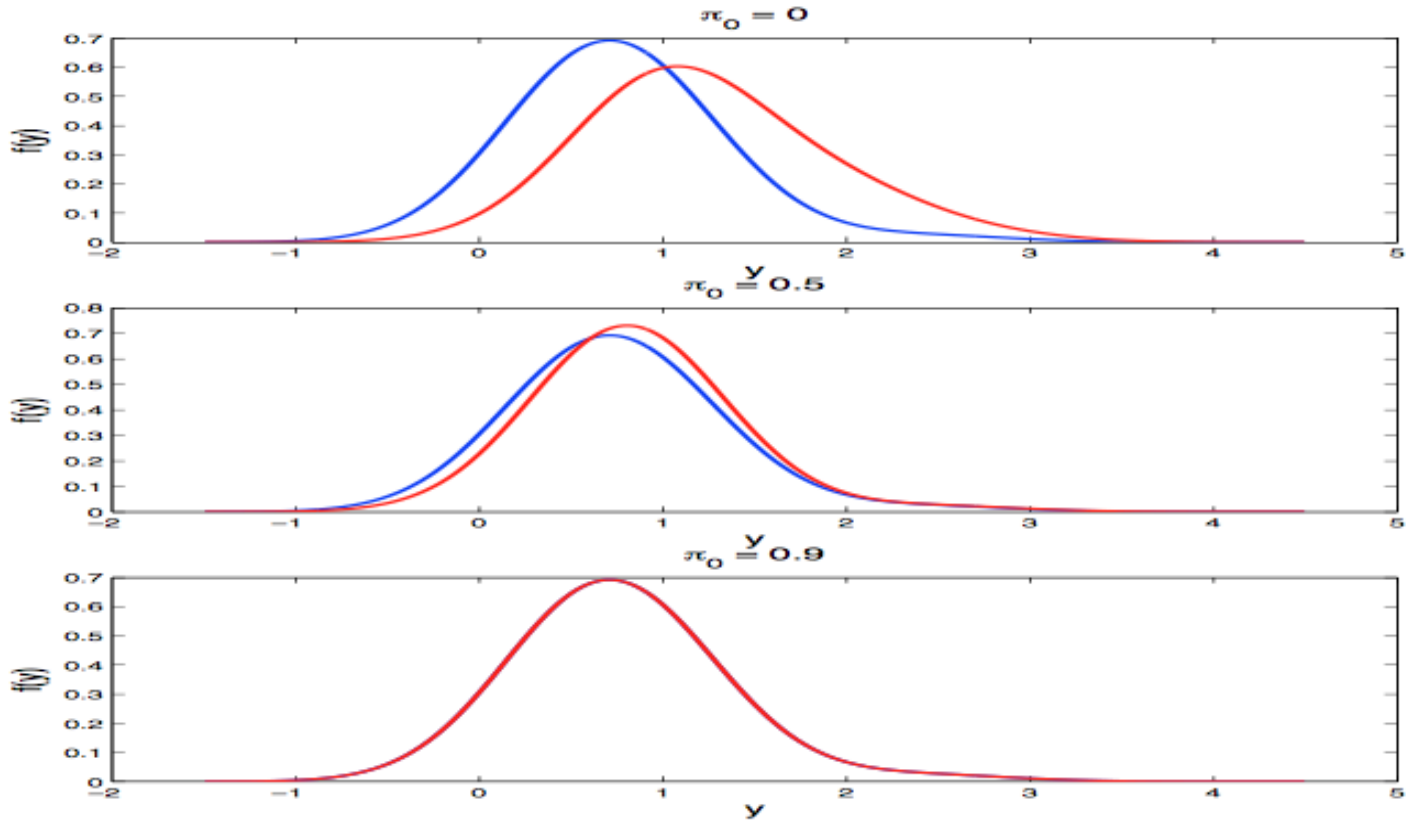
One draw from the rDDP



rDDP Mixtures

- We can use $(P_1, \ldots, P_K)$ as a collection of mixture distributions to obtain a class of rDDPM models
- Let $g_k(y) = \int K(y, \mu) dP_k(\mu)$ denote the density in group k, with $K(\cdot)$ a kernel satisfying monotone stochastic order
- Integral operator induces mapping from $C_E \to \mathcal{L}_E$, with $(P_1, \ldots, P_K) \in C_E \& (g_1, \ldots, g_K) \in \mathcal{L}_E$.
- For normal $K(\cdot)$, $\mathcal{L}_E$ contains all $K \times 1$ collections of densities satisfying partial ordering E in its closure

One draw from the rDDPM



Hypothesis Testing - 2 Group Case

- Hypothesis testing of equalities in distributions, g_1, g_2, against stochastically ordered alternatives
- Differences in g_1, g_2 controlled through differences in mixture distributions P_1, P_2
- In two group case, focus on interval null based on TV distance

$$d_{12} = \max_{B \in \mathcal{B}} |P_1(B) - P_2(B)|$$

- With $\beta_h = \Theta_{2h} - \Theta_{1h}$,
  $d_{12} = \sum_{h=1}^{\infty} \pi_h 1_{(\beta_h > 0)} \sim \text{Beta}(\alpha(1-\pi_0), \alpha\pi_0)$
- Hypotheses: $H_0 : d_{12} \leq \epsilon, H_1 : d_{12} > \epsilon$.

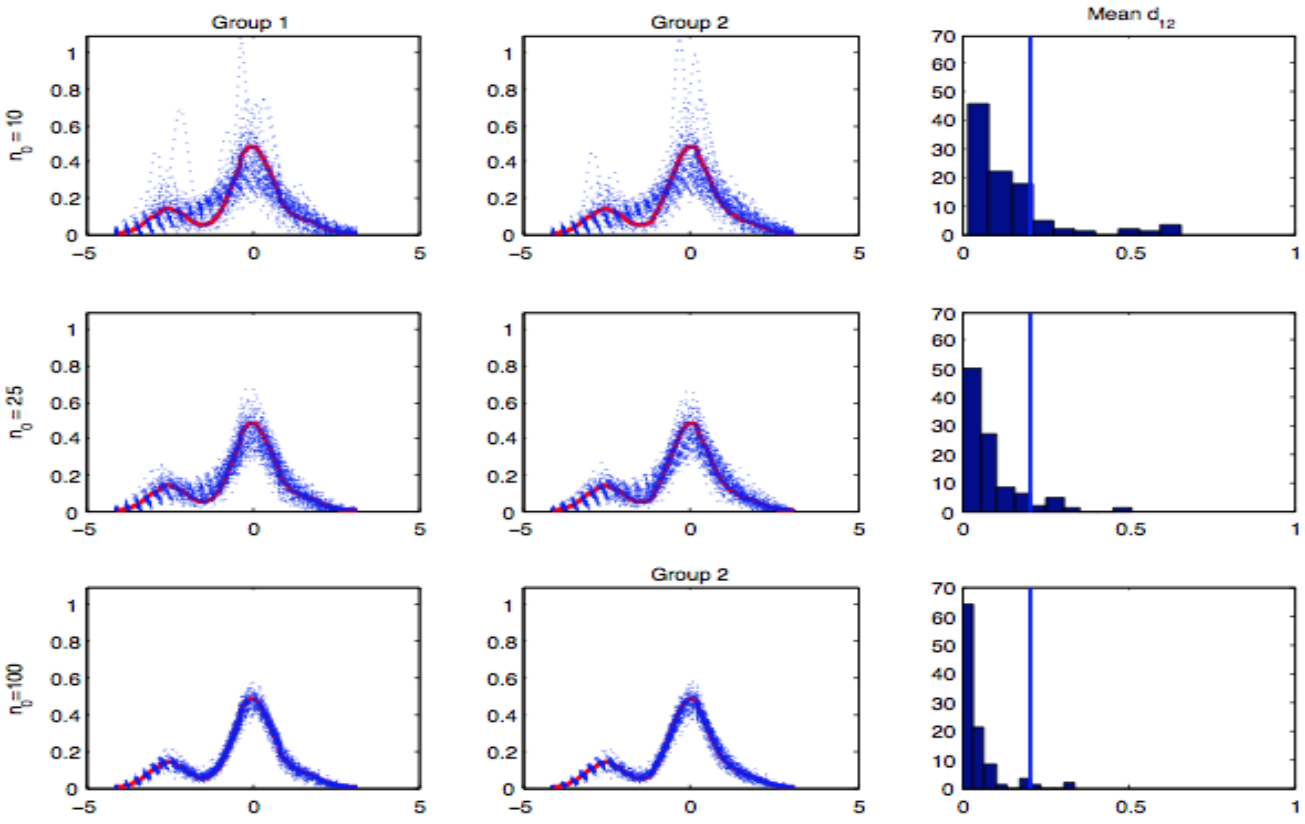
Multiple Groups & Computation

- Extensions to multiple groups & censored data are trivial
- Posterior computation can proceed via a highly-efficient & simple blocked Gibbs sampler (Ishwaran & James, 01)
- We ran a simulation study to assess frequentist operating characteristics

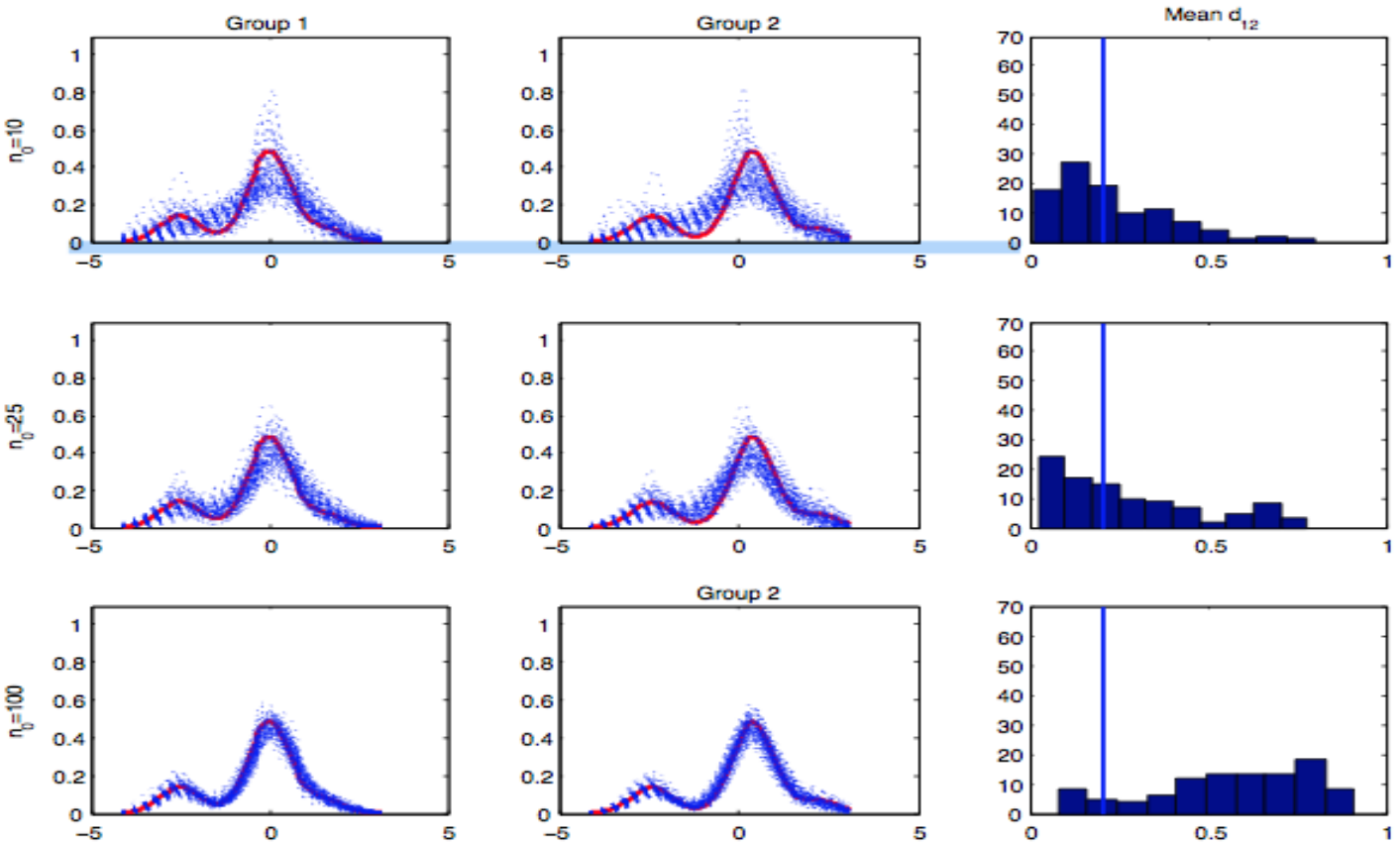
Simulation study ($K = 2$)

- Case 1: Both Group 1 and Group 2 generated from $f(y) = 0.2N(y; -2.5, \tau^{-1}) + 0.7N(y; 0, \tau^{-1}) + 0.1N(y; 1.5, \tau^{-1})$, $\tau = 3$
- Case 2: Change the component-specific means $(-2.4, 0.4, 2.2)$.
- Simulated 100 datasets under three sample sizes, $10, 25$ and 100.
- Fix ϵ, choose π_0 such that $P(d_{12} < \epsilon) = 0.5$.

Simulation results (Case 1)



Simulation results (Case 2)



Sensitivity to ϵ

Table 1. *Simulation study. Summary statistics of d_{12} across the simulations for each sample size. Results shown are means with 95% empirical confidence limits in parentheses*

Case	Common sample size	d_{12}	$\text{pr}(d_{12} < \epsilon \mid \text{data})$ $\epsilon = 0{\cdot}01$	$\epsilon = 0{\cdot}05$	$\epsilon = 0{\cdot}1$
1	10	0·140	0·67	0·72	0·75
		(0·028, 0·614)	(0·17, 0·86)	(0·18, 0·91)	(0·22, 0·93)
1	25	0·085	0·72	0·78	0·81
		(0·011, 0·299)	(0·19, 0·89)	(0·22, 0·94)	(0·28, 0·96)
1	100	0·044	0·79	0·85	0·89
		(0·003, 0·215)	(0·28, 0·94)	(0·30, 0·99)	(0·42, 1·00)
2	10	0·233	0·55	0·60	0·63
		(0·029, 0·660)	(0·10, 0·82)	(0·10, 0·91)	(0·10, 0·93)
2	25	0·278	0·46	0·51	0·54
		(0·032, 0·765)	(0·02, 0·84)	(0·02, 0·87)	(0·06, 0·91)
2	100	0·560	0·13	0·15	0·18
		(0·091, 0·884)	(0·00, 0·74)	(0·00, 0·79)	(0·00, 0·83)

DNA Repair Studies Application

- Interest in identifying genes predictive of DNA repair rates for individuals in Environmental Genome Project
- Frequency of strand breaks on individual cell level measured at baseline, after induced damage & after repair
- Initially study assessed impact of dose of H_2O_2 & repair time using samples of 100 cells from single subject

DNA Repair Studies Application

- Batches of cells were exposed to $0, 5, 20, 50$ or 100μ mol of H_2O_2 (hydrogen peroxide)
- DNA damage was then measured in individual cells after allowing a repair time of $0, 60$ or 90 min.
- x_i for cell i: Olive tail moment, surrogate of the frequency of DNA strand-breaks obtained using the comet assay.
- Let $a_i \in \{1, \ldots, K\}$ be a group index denoting the level of H_2O_2 and repair time for cell i.
- The value of a_i for each dose $\times$ repair time value is shown in Fig. 3.
- The total sample size is 1400, with 100 observation per group except for groups 9 and 13, which had 50.

DNA Repair Studies Application

- Among cells with zero repair time, DNA damage should be nondecreasing with the dose of H_2O_2.
- In addition, within a given dose level, DNA damage should be non-increasing with repair time.
- we make the ordering assumption illustrated in Fig. 3 using a directed graph, with arrows pointing towards stochastically larger groups.
- We wish to assess whether or not DNA damage continues to increase at higher levels of H_2O_2 exposure, and investigate whether or not damage is significantly reduced across each increment of the repair time.

Directed graph indicating stochastic order

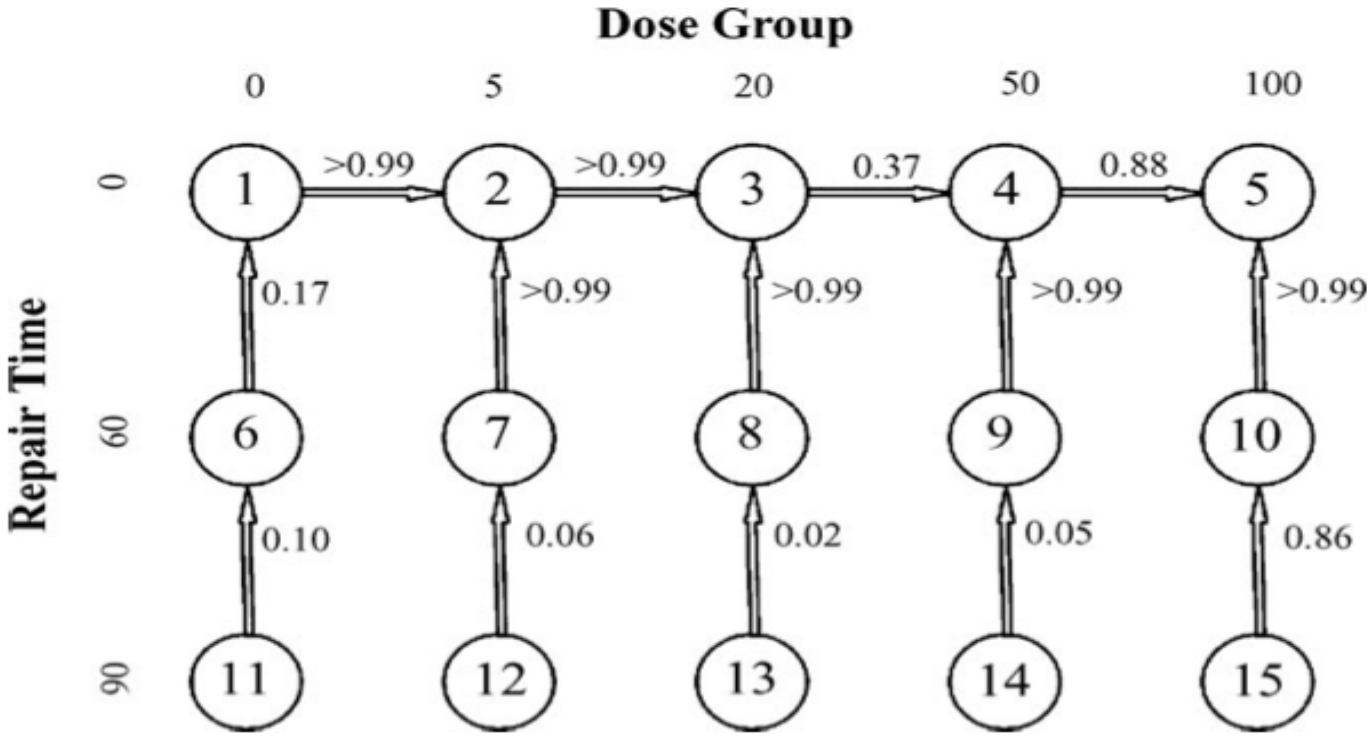
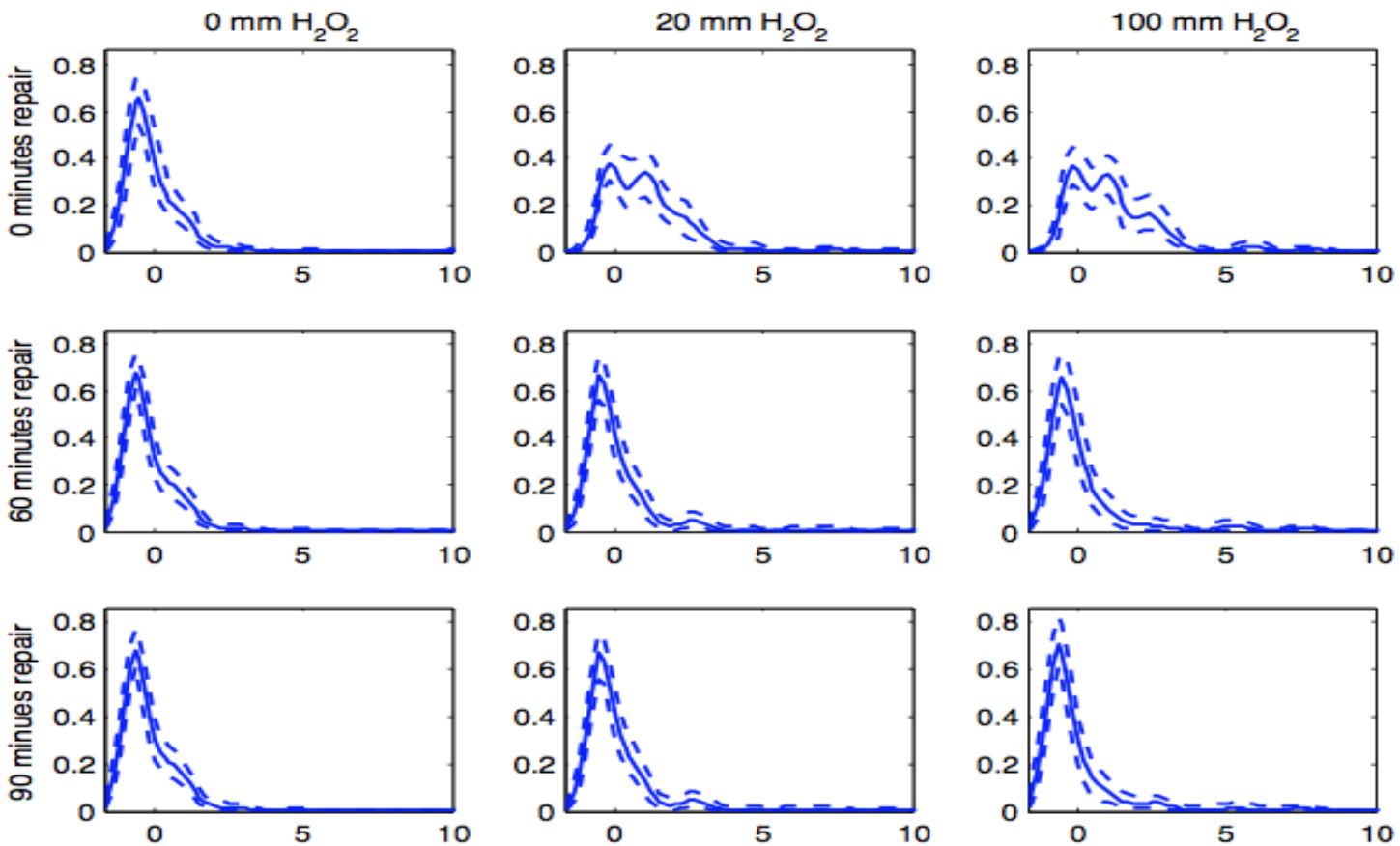


Fig. 3. Genotoxicity application. Directed graph illustrating order restriction. Arrows point towards stochastically larger groups. Posterior probabilities of H_{1k} are shown.

Results for Genotoxicity Application



Discussion

- Bayesian method for testing differences among groups against stochastically ordered alternatives
- Also allows estimation of densities (or pmfs) in each group
- Covariates can be included & approach can be embedded in hierarchical model (allowing censoring, missing data, multivariate observations of latent variable, etc)
- Allow stochastic ordering with continuous predictors?

Stochastic Ordering with Continuous Predictors (Wang & Dunson, 07)

- Generalize estimation & testing methods to continuous predictors
- Let $\mathcal{P}_{\mathcal{X}} = \{(P_x, x \in \mathcal{X}) : P_x \in \mathcal{P}, x \in \mathcal{X}\}$, $P =$ set of probability measures on $\mathcal{B}(\mathcal{U}), \mathcal{U}, \mathcal{X} =$ subsets of $\mathbb{R}$
- Need to define a prior for $\mathcal{P}_{\mathcal{X}}$ with support on

$$C_{\mathcal{X}} = \{(P_x, x \in \mathcal{X}) \in \mathcal{P}_{\mathcal{X}} : P_x \precsim P_{x'}, x \leq x', x, x' \in \mathcal{X}\}.$$

- How to accomplish, while having simple computation & hypothesis testing?

Mixing over Extreme Points

- Lemma 1 - $C_{\mathcal{X}}$ = weakly closed convex set $\rightarrow$ any elements of $C_{\mathcal{X}}$ expressed as mixture over the extreme points
- Lemma 2 - the extreme points of $C_{\mathcal{X}}$ are $ex\{C_{\mathcal{X}}\} = \{(\delta_{s(x)}, x \in \mathcal{X}) : s \in \mathcal{S}_{\mathcal{X}}\}$, where $\mathcal{S}_{\mathcal{X}}$=space of non-decreasing functions
- Theorem 1: For any $P \in C_{\mathcal{X}}$ there exists a mixture measure Q such that $(P_x, x \in \mathcal{X}) = \int_{\mathcal{S}_{\mathcal{X}}} (\delta_{s(x)} : x \in \mathcal{X}) dQ(s)$.
- Prior for Q on $\mathcal{S}_{\mathcal{X}}$ induces prior for P on $C_{\mathcal{X}}$!

Proposed rDDP Mixture Model

- Motivated by this theory, we choose the rDDP prior:

$$P_x = \sum_{h=1}^{\infty} \pi_h \delta_{\Theta_h(x)},$$

  where $\theta_h \sim Q_0$ and Q_0 has support on $\mathcal{S}_{\mathcal{X}}$.
- The "atoms" in the Dirichlet process correspond to non-decreasing stochastic processes
- Monotone splines (Ramsay, 1988) for the functional atoms
- Letting $f(y|x) = \int N(y; \mu, \sigma^2) dP_x(\mu)$,obtain a method for isotonic density regression

Local & Global Hypothesis Testing

- We consider the following local null and alternative:

$$H_0(x, x') : d_{TV}(x, x') < \epsilon \quad vs. H_1(x, x') : d_{TV}(x, x') \geq \epsilon,$$

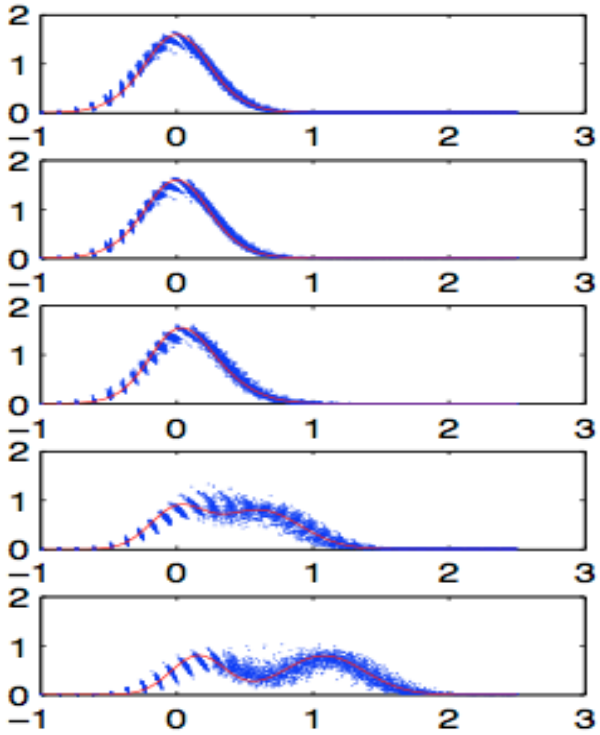
with $d_{TV}(x, x') = sup_{y \in \mathbb{R}} |F_x(y) - F_{x'}(y)|$

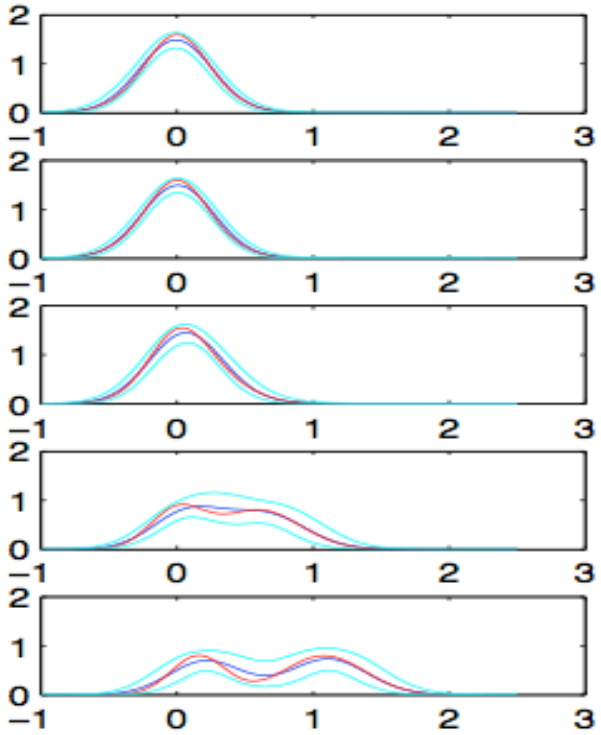
- Local null $H_0(x, x') \rightarrow$ effectively no change between x and x'
- Global null formulated as intersections of local nulls
- $H_0(0, x) = \cap_{x' < x} H_0(x, x')$.

Simulation Study

- To assess performance, we ran a simulation study with 200 datasets have size $n = 500$
- The response variable y was generated from a mixture of two normals, with no association for $x \in [0, 0.3]$ & a non-linear association in $x \in [0.3, 0.7]$
- Two normal components had different polynomial regressions in the mean

Simulation Study Results - Conditional Densities





Simulation Study Results - local testing