

Bayesian Wavelet-Based Modeling of Hierarchical Functions

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Outline

Introduction

- Architecture of Colon
- Colon Carcinogenesis Studies
- Hierarchical Functional Model

Wavelet Space Model

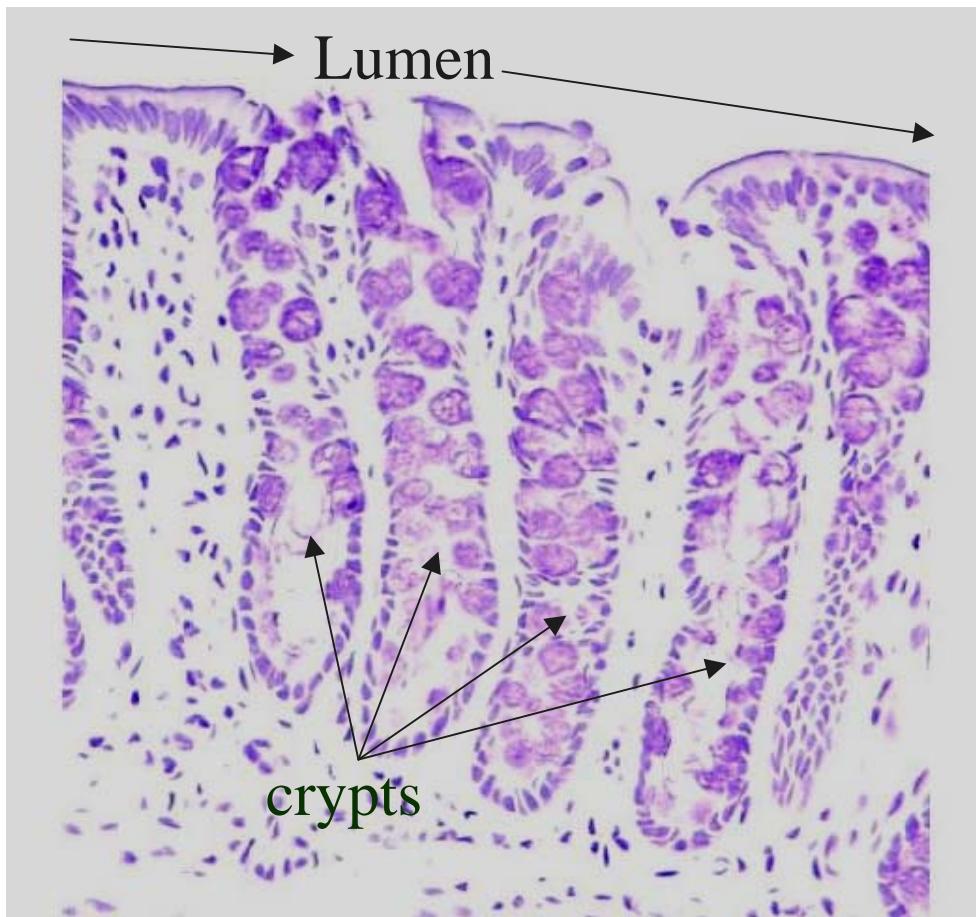
Model Fitting Issues

Results

Sensitivity Analysis

Conclusion

Architecture of Colon



-  **Stem Cells:**
Mother cells near
crypt base
-  Depth in crypt ~
age of cells
-  **Relative Cell Position**
(Depth w/in crypt):
 $t \in (0,1)$

Colon Carcinogenesis Studies



- Rats fed different diets, exposed to carcinogen, then euthanized.
- DNA adducts, DNA repair, apoptosis quantified as staining intensities
- Data has hierarchical structure
 - Treatment groups - rats - crypts - cells/pixels
 - Hierarchical Longitudinal Data

Example: Data

- Fish oil diet protective compared with corn oil diet
- DNA repair enzyme
 - 2 diets (fish/corn) x 5 times (0h,3h,6h,9h,12h)
 - 3 rats per diet x time combination
 - ~ 25 crypts per rat,
 - function sampled at $256=2^8$ equally spaced t
- Interested in:
 - Estimation/inference on diet/time profiles
 - Estimation of individual rat/crypt profiles
 - Estimation of relative variability at hierarchical levels

Hierarchical Functional Model

2-level HF model:

$$\mathbf{Y}_{abc} = g_{abc}(t) + \mathbf{e}_{abc},$$

$$g_{abc}(t) = g_{ab}(t) + \eta_{abc}(t)$$

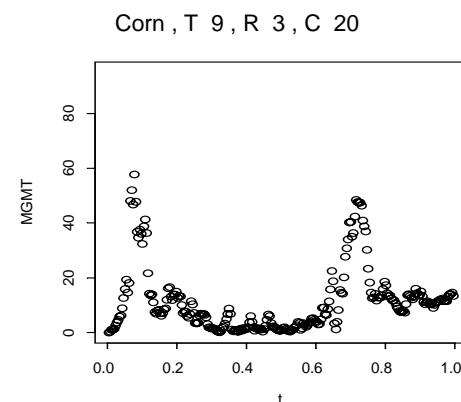
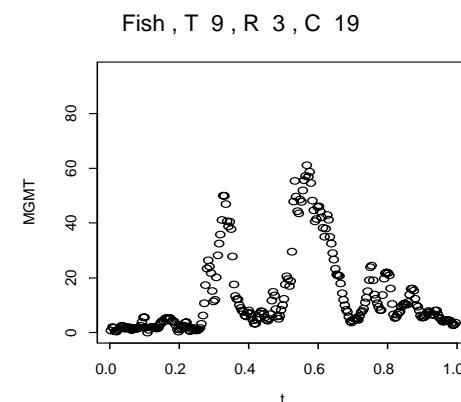
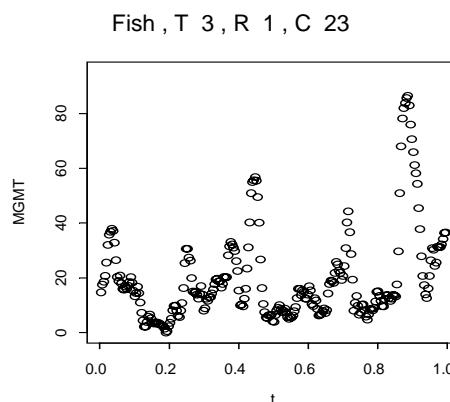
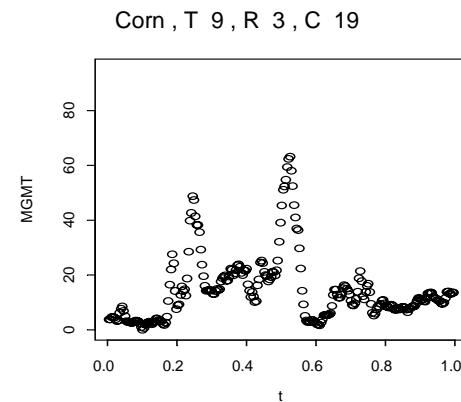
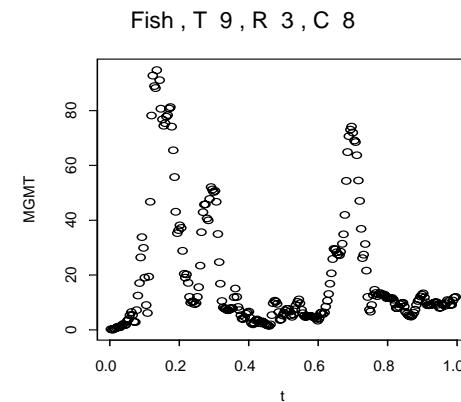
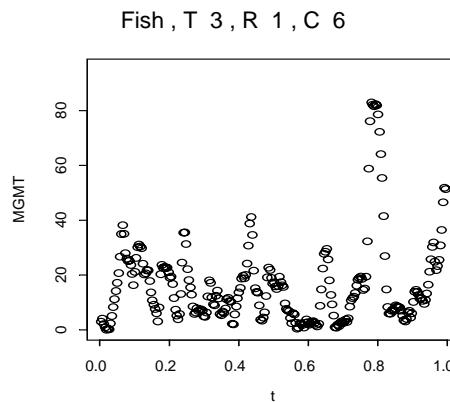
$$g_{ab}(t) = g_a(t) + \xi_{ab}(t)$$

where $\mathbf{e}_{abc} \sim MVN(\mathbf{0}, \sigma_e^2 \mathbf{I})$,

$\eta_{abc}(\bullet)$ and $\xi_{ab}(\bullet)$: mean 0 with covariance
matrices $\Sigma_1(t_1, t_2)$ and $\Sigma_2(t_1, t_2)$.

DNA Repair Data

DNA Repair Enzyme for Selected Crypts



Wavelet Space Model

Wavelets: families of orthonormal basis functions

$$\mathbf{d}_{abc} = \{d_{abc}^{j,k}\} = \mathbf{W} \mathbf{y}_{abc}$$

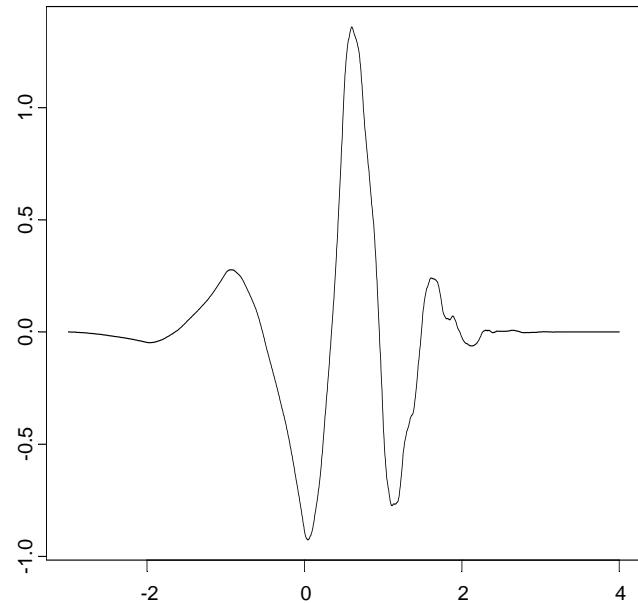
Discrete Wavelet Transform

$$d_{abc}^{j,k} \sim N(\theta_{abc}^{j,k}, \sigma_e^2)$$

$$\theta_{abc}^{j,k} \sim N(\theta_{ab}^{j,k}, \sigma_{1,j}^2)$$

$$\theta_{ab}^{j,k} \sim N(\theta_a^{j,k}, \sigma_{2,j}^2)$$

Daubechies Basis Function



“Shrinkage” Prior

¶ Prior on $\theta_a^{j,k} \Rightarrow$ Normal-0 mixture

$$\theta_a^{j,k} \sim N(0, \gamma_a^{j,k} \tau_j^2)$$

$$\gamma_a^{j,k} \sim \text{Bernoulli}(p_j)$$

¶ Nonlinear shrinkage -- denoises data

¶ p_j and τ_j^2 - regularization parameters
(scale dependent shrinkage)

¶ Smaller p_j : More smoothing at scale 2^{j-1}

Model Fitting



Hierarchical model fit using MCMC

- Performed on marginalized model
- Steps: $(\Omega^j = \text{VCs at wavelet level } j)$

1. Sample $\theta_a^{j,k}$ from $(\theta_a^{j,k} | \mathbf{d}_a^{j,k}, \Omega^j)$ for each j, k, a
 - Mixture of point mass at 0 and Normal
2. Sample Ω^j from $(\Omega^j | \mathbf{d}^{j,k}, \theta_a^{j,k})$ for each j
 - Metropolis step used



IDWT applied to samples of $\{\theta_a^{j,k}\}$ yield posterior samples of $g_a(t)$.

Model Fitting

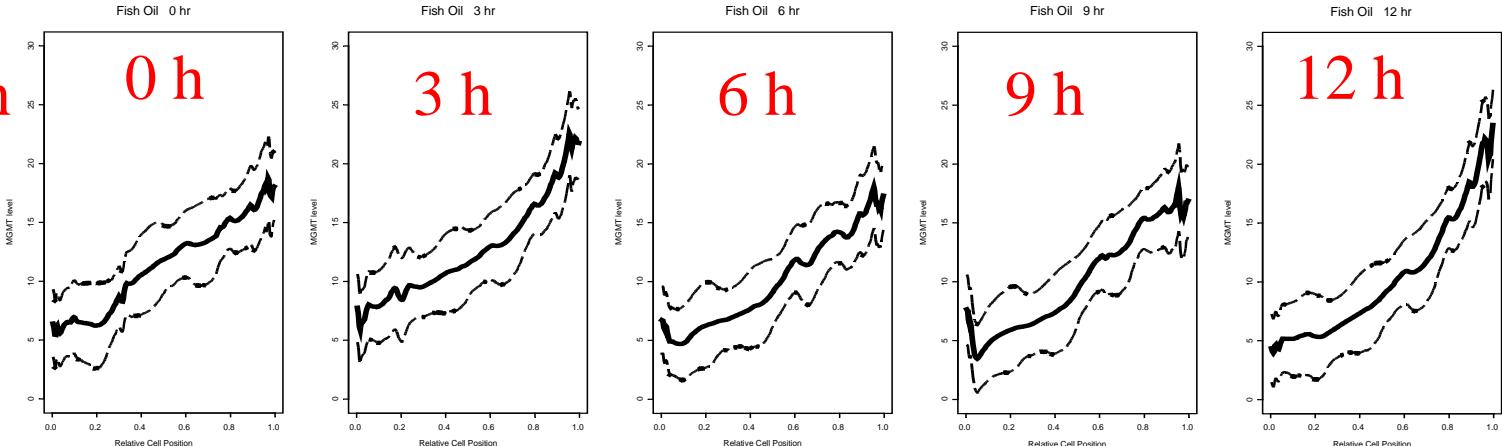
- Relative variability at hierarchical levels, measured by trace, given directly by wavelet space variance components.
- Can also obtain posterior samples of profiles for rats and crypts.

1. Sample from $(\theta_{ab}^{j,k} | \theta_a^{j,k}, \Omega^j, \mathbf{d}_{ab}^{j,k})$ for each a, b, j, k
2. Sample from $(\theta_{abc}^{j,k} | \theta_{ab}^{j,k}, \Omega^j, \mathbf{d}_{abc}^{j,k})$ for each a, b, c, j, k

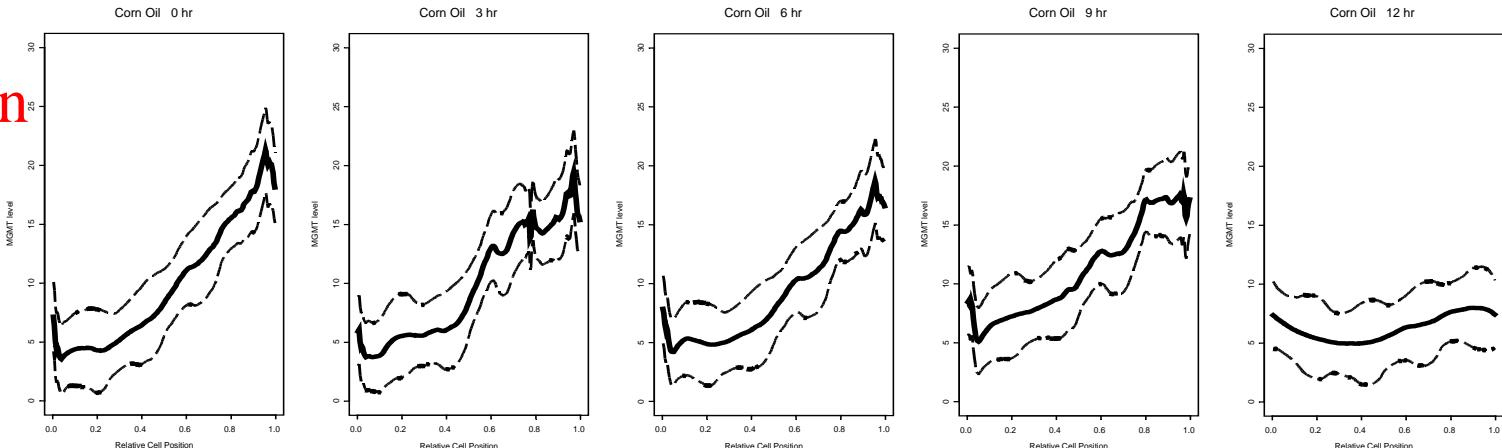
Results: DNA Repair Enzyme

Estimates & 90% posterior bounds by diet/time

Fish
Oil

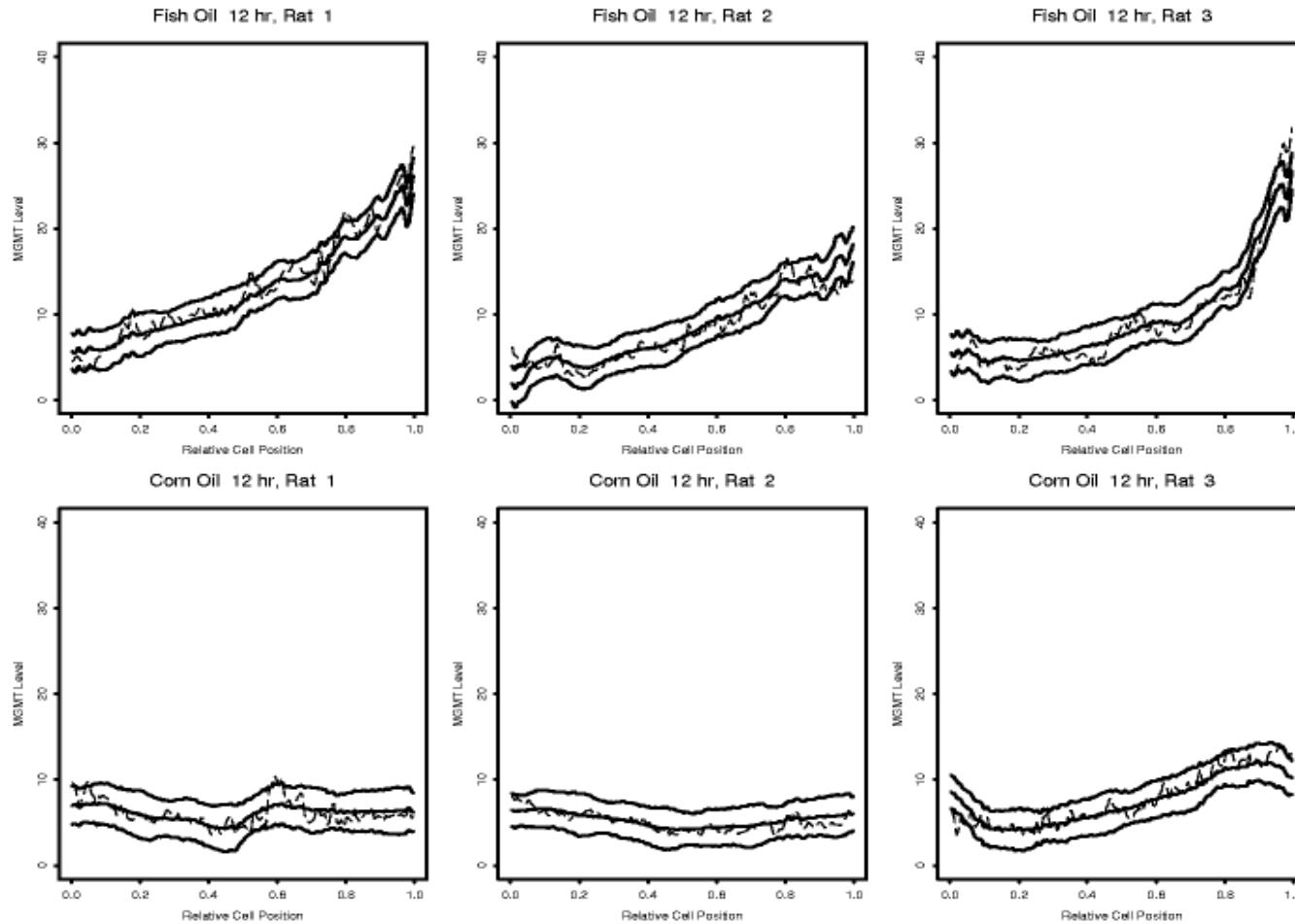


Corn
Oil



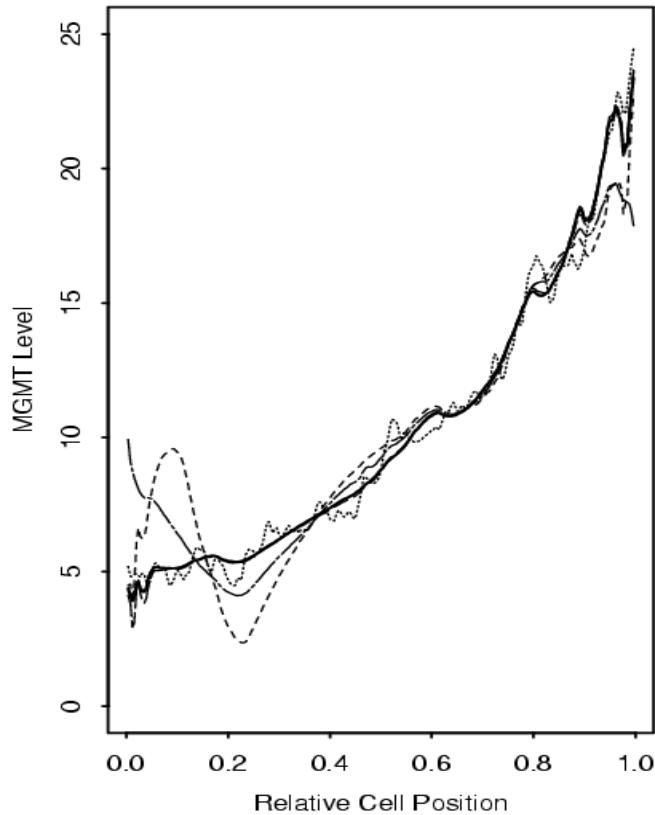
Results: DNA Repair Enzyme

Estimates of individual rat profiles for T12 rats

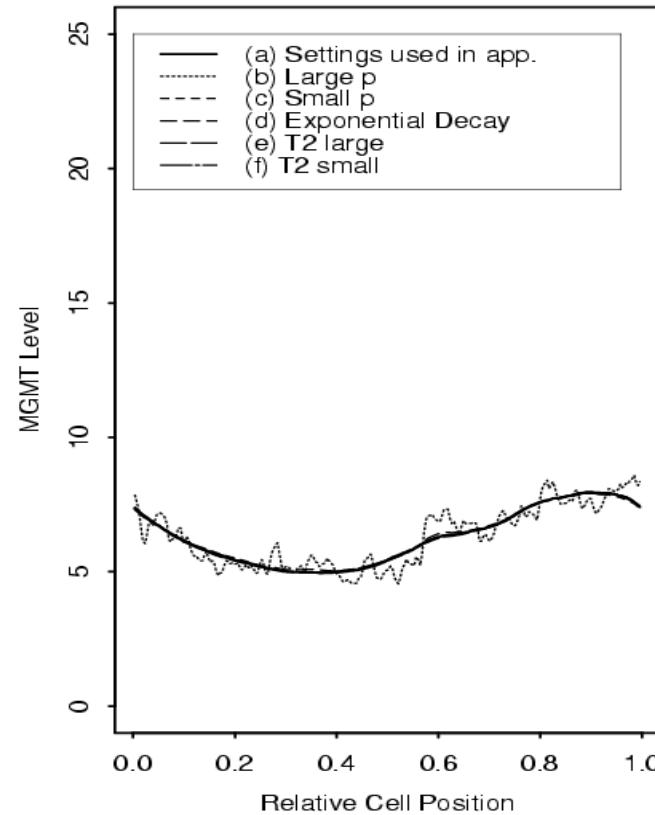


Sensitivity Analysis

Fish Oil, T12



Corn Oil, T12



Choice of Smoothing Parameters

Shrinkage Function:

$$h(Z, T_j^2, p_j) = \underbrace{\left(\frac{T_j^2}{T_j^2 + 1} \right)}_{\text{Linear Shrinkage}} \underbrace{\Pr\left\{ \gamma_a^{j,k} = 1 \mid \mathbf{d}_a^{j,k} \right\}}_{\text{Nonlinear Shrinkage}}$$

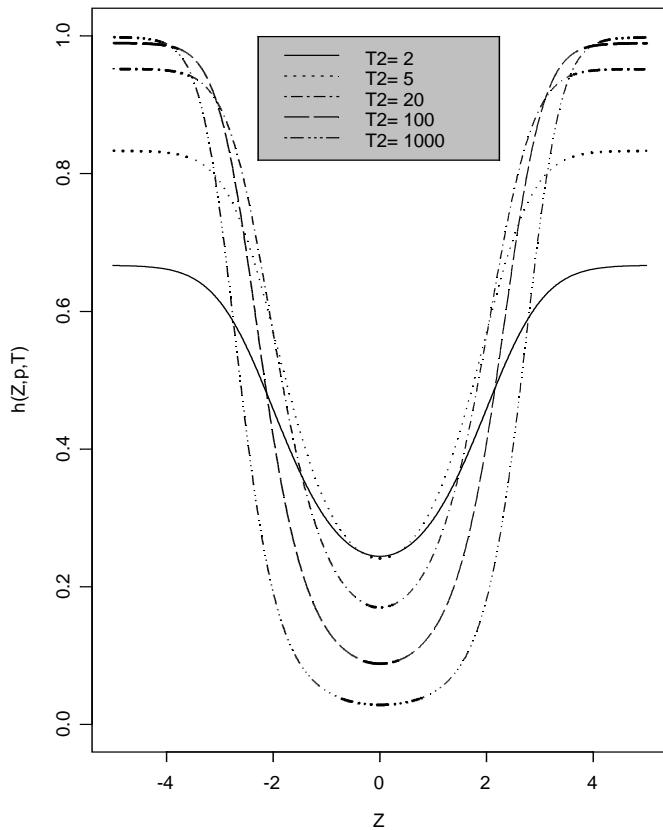
$$\Pr\left(\gamma_a^{j,k} = 1 \mid \mathbf{d}_a^{j,k} \right) = \frac{O}{O+1}, \quad O = \text{Posterior Odds}$$

$$\underbrace{O}_{\text{Posterior Odds}} = \underbrace{\left(\frac{p_j}{1-p_j} \right)}_{\text{Prior Odds}} \underbrace{\left(1 + T_j^2 \right)^{-1}}_{\text{Bayes Factor}} \exp\left\{ \frac{Z^2}{2} \left(\frac{T_j^2}{T_j^2 + 1} \right) \right\}$$

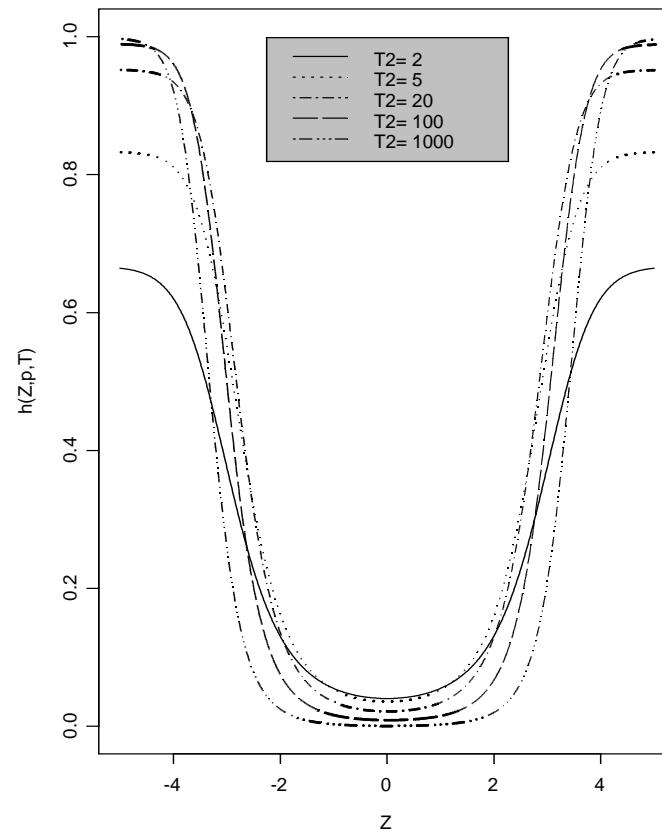
$$Z = \hat{\theta}_{a,NS}^{j,k} / \sqrt{\text{Var}(\hat{\theta}_{a,NS}^{j,k})} \quad T_j^2 = \tau_j^2 / \text{Var}(\hat{\theta}_{a,NS}^{j,k})$$

Shrinkage Curves

(a) Shrinkage functions for $p = 0.5$



(b) Shrinkage functions for $p = 0.1$



Conclusions

- Method to fit hierarchical longitudinal data
 - Nonparametrically estimate profiles at mean, individual and subsampling levels using wavelet shrinkage.
 - Covariance parameter estimates
- Posterior samples from MCMC allow inference to be done
- All done with unified, ‘nonparametric’ model that appropriately adjusts for imbalance & correlation.
- Wavelets allow use of simpler covariance structures and spatially heterogeneous functions
- Can be generalized to more complex covariance structures