Spatio-Temporal Threshold Models for Relating UV Exposures and Skin Cancer in the Central United States

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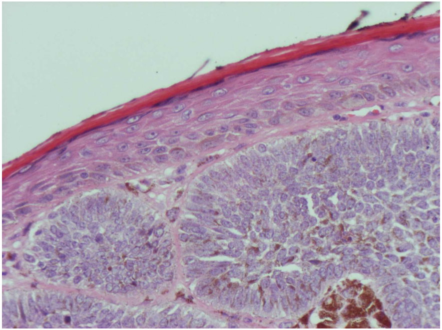
Motivation



Basal Cell Carcinoma, ©DermAtlas

most common form of *non-melanoma skin cancer* (NMSC)

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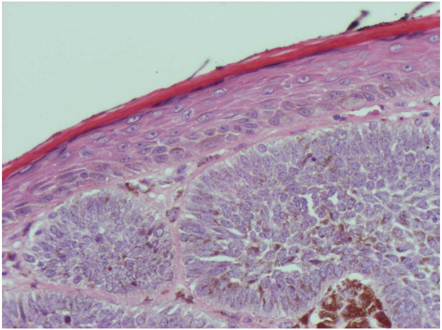

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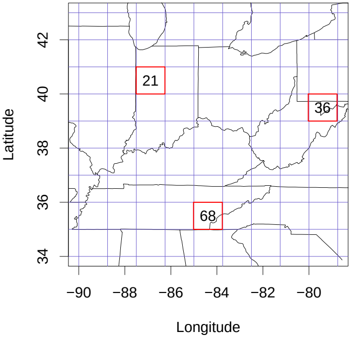
most common form of *non-melanoma skin cancer* (NMSC)
associated with exposure to ultraviolet (UV) radiation

Data Sources

Cancer Outcome Data: from the United States Radiologic Technologists (USRT) cohort



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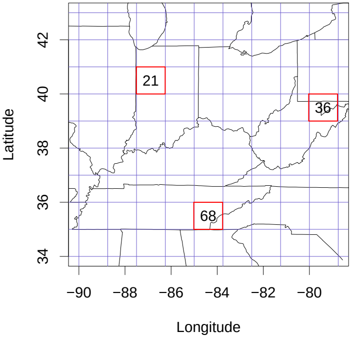

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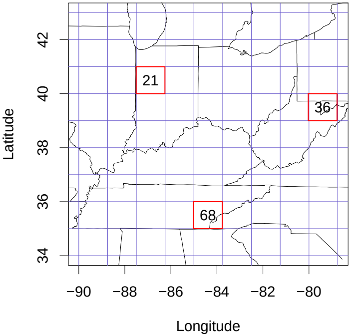

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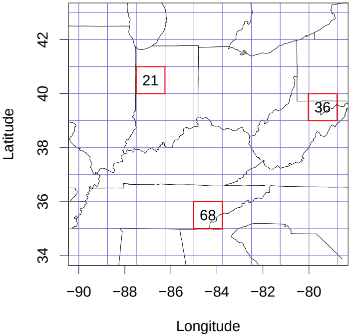
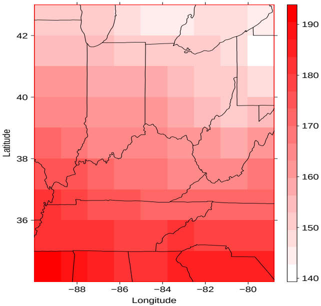


- Cohort: $> 100,000$ US radiation techs
- Our Subsample: $19,081$ living in this square $<$ age 13
- Our Cases: 383 (2.0%) SCC, 1283 (6.7%) BCC, 1495 (7.8%) NMSC (171 both)

Data Sources

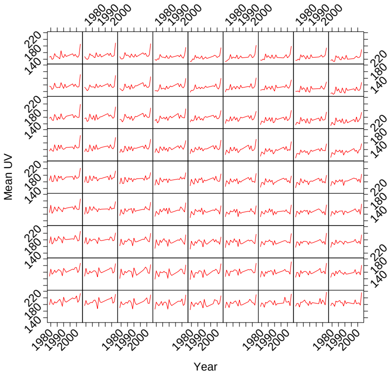
Exposure Data: from the Total Ozone Mapping Spectrometer (TOMS) project

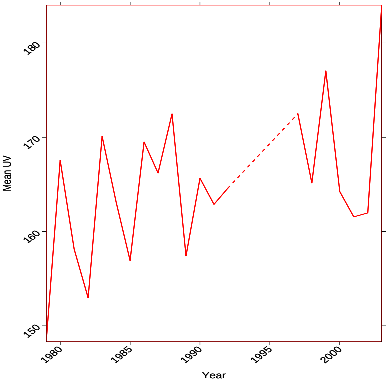


Average Erythemal UV Dose, 1979

UV erythemal dose (milli-watts/m^2)

Data Sources





UV Dose Data by Grid

Enlarged Time Plot of a Single Grid

Note the missing years and the latitude trend; the enlarged grid on the right is the very middle one on the left

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- W_1: Year (1979-2003, centered)
- W_2: Latitude (34.5 to 42.5, centered).

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$$\mu_{ij} = \mu_0 + \gamma_{0i} + (\mu_1 + \gamma_{1i}) W_{1j} + \alpha W_{2i}$$

- Drop random slopes, add spatially-structured prior on random intercepts

$$\mu_{ij} = \mu_0 + \gamma_{0i} + \mu_1 W_{1j} + \alpha W_{2i};\ \gamma_0 \sim CAR(\tau_0)$$

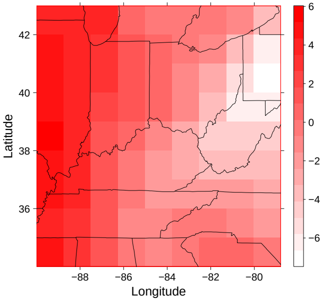
Results I: Spatiotemporal UV Dose

Model	$\overline{D}$	$\hat{D}$	p_D	DIC
Simple linear	715.50	552.50	163.02	878.50
Random effects	650.40	567.30	83.06	733.50
+ Latitude	650.20	582.40	67.81	718.00
+ CAR prior	621.50	579.40	42.04	*663.50*

Model	MSEP (1979)	MSEP (1992)	MSEP (3 grids)
Simple linear	159.51	83.70	NA
Random effects	140.86	80.65	400.00
+ Latitude	145.06	81.27	144.27
+ CAR prior	*140.12*	*79.49*	*121.51*

Model comparison, spatiotemporal UV models.

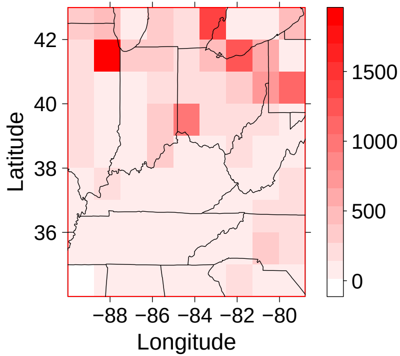
Results I: Spatiotemporal UV Dose



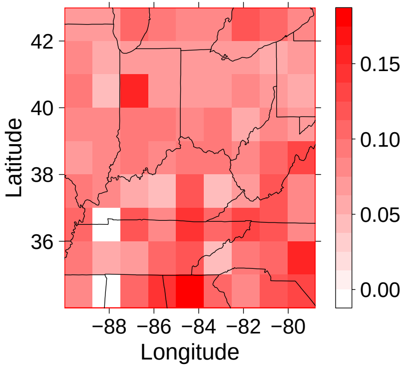
Map of fitted spatially structured random intercepts (γ_{0i})

Parameter	Mean	95% Credible Interval
μ_0 (Intercept)	166.80	[166.40, 167.10]
α (Latitude)	-4.76	[-5.40, -4.19]
μ_1 (Year)	0.59	[0.55, 0.64]
σ_0 (Spatial sd)	3.82	[3.04, 4.75]
σ (Error sd)	7.37	[7.13, 7.62]

Data II: Cancer and Average UV Dose



Cohort Members



NMSC Cumulative Incidence Rate

Models II: Cancer and Average UV Dose

We wish to model the NMSC outcome for the k^{th} person, Z_k, as a function of the following covariates:

- X_1: Age ($\in [43, 94]$, centered)
- X_2: Sex (female=1, male=–1)
- X_3: Number of blistering sunburns ($\in [0, 198]$, centered)
- X_4: Complexion (light=1, other=–1)
- X_5: Average UV dose under age 13
- X_6: Hours spent in summer sun (cumulative under age 13)

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Since the UV exposure trajectories do not cross over time, we may take X_5 as the fitted exposure at any time point for k's grid square

We also considered multiplicative interaction between UV dose and hours in the sun

Models II: Cancer and Average UV Dose

The DIC-best model:

$$
\begin{aligned}
\textit{Stage 1:} \quad & Y_{ij} \sim \textit{Normal}(\mu_{ij}, \sigma^2) \\
& \mu_{ij} = \mu_0 + \gamma_{0i} + \alpha W_{2i} + \mu_1 W_{1j};\ \boldsymbol{\gamma}_0 \overset{iid}{\sim} \textit{CAR}(\tau_0) \\
\textit{Stage 2:} \quad & Z_k \sim \textit{Bernoulli}(p_k) \\
\textit{logit}(p_k) & = \beta_0 + \beta_1 X_{1k} + \beta_2 X_{2k} + \beta_3 X_{3k} + \beta_4 X_{4k} \\
& \quad + \beta_5(\gamma_{0g_k} + \alpha W_{2g_k}) + \beta_6 X_{6k}\ ,
\end{aligned}
$$

where g_k is k's childhood grid square

Results II: Cancer and Average UV Dose

Parameter	Mean	95% Credible Interval
β_0 (Intercept)	-2.473	$[-2.552, -2.396]$
β_1 (Age)	0.054	[0.049, 0.060]
β_2 (Sex)	0.012	$[-0.056, 0.079]$
β_3 (Blistering sunburns)	0.022	[0.017, 0.027]
β_4 (Complexion)	0.328	[0.273, 0.384]
β_5 (Average UV dose)	0.013	[0.008, 0.017]
β_6 (Hours in sun)	0.046	$[-0.010, 0.101]$

Stage 2 posterior parameter estimates

- The UV dose variable has mean 166.3 and sd 15.4, so 1 sd change is .013*15.4 = .20 on the logit scale
- Hours in sun (β_6) is not quite significant, but trend is positive

Models III: Cancer and Peak UV Dose

We now wish to model NMSC outcome (Z) of the k^{th} person as a function of peak UV dose, $X_5(g_k, C)$, i.e., the historical average proportion of summer days $\geq C$ in the k^{th} person's childhood grid square, g_k, where the threshold C is estimated from the data.

We considered the same model variations as above.

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We considered the same model variations as above.

The best model (according to DIC and 10% holdout predictive ability):

$$\begin{aligned} Z_k &\sim Bernoulli(p_k) \\ logit(p_k) &= \beta_0 + \beta_1 X_{1k} + \beta_2 X_{2k} + \beta_3 X_{3k} + \beta_4 X_{4k} \\ &\quad + \beta_5 X_5(g_k, C) + \beta_6 X_{6k} \end{aligned}$$

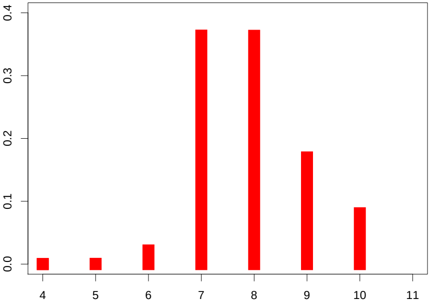
Results III: Cancer and Peak UV Dose

Parameter	Mean	95% Credible Interval
β_0 (Intercept)	-2.475	$[-2.555, -2.397]$
β_1 (Age)	0.054	[0.049, 0.060]
β_2 (Sex)	0.013	$[-0.056, 0.083]$
β_3 (Blistering sunburns)	0.022	[0.017, 0.027]
β_4 (Complexion)	0.329	[0.273, 0.385]
β_5 (Peak UV dose)	1.594	[0.864, 2.847]
β_6 (Hours in sun)	0.046	$[-0.009, 0.101]$
C (Exposure threshold)	6.842	[5, 9]

posterior parameter estimates

- Childhood peak UV dose (β_5) is positively associated with risk
- Hours in sun (β_6) is not significant, but trend is positive

Results III: Cancer and Peak UV Dose



Posterior density of the UV Index threshold (C)

- WHO categories: Low $(0-2)$, Moderate $(3-5)$, High $(6-7)$, Very High $(8-10)$, Extreme $(11+)$
- "Above 7" recommendations: avoid midday sun, seek shade, and use all protective measures (clothing, hat, sunscreen)
- Posterior distribution favors UV Index values in the High to Very High categories for NMSC risk

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Considered 2 versions of IR exposure:

- Lifetime cumulative (until diagnosis or censoring)
- Year-averaged (by number of years worked)

Both strongly related to age ($\rho \approx .5$), via first year worked (for both) and number of years worked (cumulative only).

Note: All of the following results use the entire nationwide USRT cohort of $n = 66,565$ participants

Models IV: UV + IR, Logistic

- Covariates
  - X_1: Age (centered)
  - X_2: Male (1, female$= -1$)
  - X_3: Acute sun sensitivity (1, -1 otherwise)
  - X_4: Light complexion (1, -1 otherwise)
  - X_5: Lifetime blistering burns (centered)
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- Exposures
  - X_7: UV < 13 yrs (centered)
  - X_8: IR (cumulative or year-averaged, log scale, centered)

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- Model: Logistic again:

$$
\begin{aligned}
Z_k &\sim Bernoulli(p_k) \\
logit(p_k) &= \beta_0 + \beta_1 X_{1k} + \beta_2 X_{2k} + \beta_3 X_{3k} + \beta_4 X_{4k} \\
&\quad + \beta_5 X_{5k} + \beta_6 X_{6k} + \beta_7 X_{7k} + \beta_8 X_{8k}
\end{aligned}
$$

Results IV: UV + IR, Logistic

Age-adjusted models yielded significant effects for UV + IR (using year-averaged IR, but not cumulative IR).

Parameter	Estimate	95% Confidence Interval
β_0 (Intercept)	-3.419	$[-3.59, -3.25]$
β_1 (Age)	0.052	[0.048, 0.055]
β_2 (Male)	0.048	[0.014, 0.082]
β_3 (Acute sun sens.)	0.339	[0.277, 0.400]
β_4 (Complexion)	0.252	[0.221, 0.282]
β_5 (Blistering burns)	0.018	[0.016, 0.021]
β_6 (Hours in sun)	0.041	[0.013, 0.069]
β_7 (UV $<$ age 13)	0.005	[0.004, 0.006]
β_8 (Average IR)	0.050	[0.013, 0.088]

- UV dose variable has sd 29.6, so effect on logit of 1 sd increase is $.00485 * 29.6 = .148$
- IR dose variable has sd 0.835, so effect on logit of 1 sd increase is $0.0504 * .835 = .042$

So UV “has a larger practical effect” on the logit!

Models V: UV + IR, Cox PH

- Two ways to define survival time outcome: time to NMSC or censoring since
  - age 18, or
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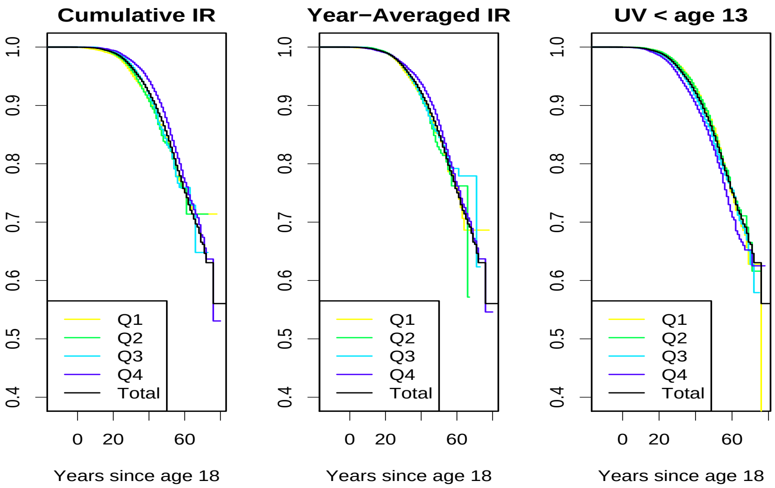
- Covariates: same as above
- Model: Cox Proportional Hazards (PH)

$$
\begin{aligned}
h(t_k|\mathbf{X}_k) &= h_0(t)\exp(\beta_2 X_{2k} + \beta_3 X_{3k} + \beta_4 X_{4k} \\
&\quad + \beta_5 X_{5k} + \beta_6 X_{6k} + \beta_7 X_{7k} + \beta_8 X_{8k})
\end{aligned}
$$

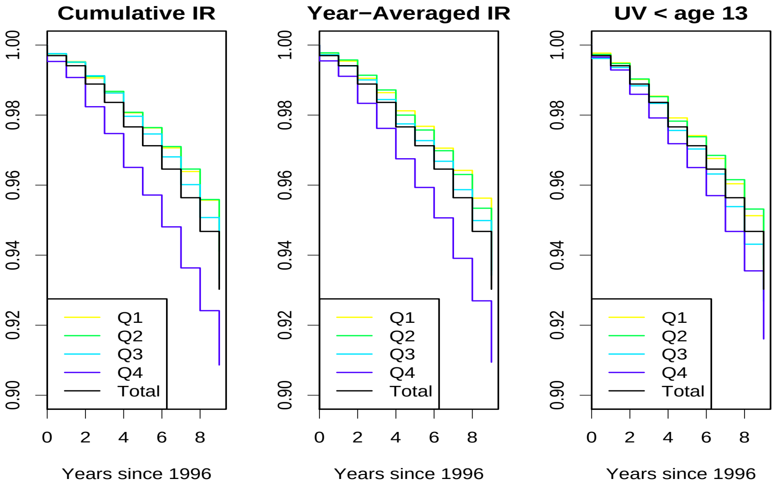
Models V: UV + IR, Cox PH

Age time scale fails to separate the survival patterns by exposure quartile:



Models V: UV + IR, Cox PH

Calendar year time scale succeeds in separating the survival curves by exposure quartile:



Results V: UV + IR, Cox PH

Cohort-type survival framework using calendar year time scale produces sensible (i.e., positive) estimates for IR risk:

Parameter	Hazard Ratio	95% Confidence Interval
β_2 (Male)	1.121	[1.078, 1.166]
β_3 (Acute sun sens.)	1.351	[1.255, 1.454]
β_4 (Light complexion)	1.219	[1.175, 1.265]
β_5 (Blistering burns)	1.013	[1.011, 1.016]
β_6 (Hours in sun < 13)	1.012	[0.978, 1.046]
β_7 (UV $<$ age 13)	1.004	[1.003, 1.005]
β_8 (Average IR)	1.352	[1.294, 1.411]

- UV dose variable has sd 29.6, so Cox HR effect of 1 sd increase is $\exp(0.00375 * 29.6) = 1.12$
- IR dose variable has sd 0.835, so Cox HR effect of 1 sd increase is $\exp(.301 * .835) = 1.29$

So IR "has a larger practical effect" on the HR!

Conclusions so far

Using USRT data from the central US:

- **UV doses increased** over the time period examined, with negligible spatial variation in time trends
- **Spatial variation** in UV dose exists after adjusting for latitude
- **Average childhood UV dose predicts cancer** (NMSC) outcomes *independently* of hours spent in sun
- **Peak childhood UV dose predicts cancer** (NMSC) outcomes best when UV Index threshold is 7 or 8 (i.e., "High to Very High")

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Using USRT data from the entire US:

- **Childhood UV + IR (avg. lifetime) exposures related to cancer** through logistic models
- **Childhood UV + IR (avg. lifetime) exposures related to cancer** through survival models provided we use a calendar year-based definition for the event time (cohort model)

Future work: Refining UV

- Refinements of the UV dose variable: Letting t indicate *continuous* time within summer, redefine UV exposure as cumulative over ages 3 to 13:

$$UV_k = \frac{1}{150} \sum_{j=1}^{m} \int_0^{150} \mu_{g_k, a_{k+j}}(t) dt \ ,$$

  where g_k indicates subject k's grid of residence at age 10, and a_k indexes the year in which k turned 2 years old

  May combine this additively or multiplicatively with annual (modeled) IR doses, contemporaneously or lagged by L years

- We also have data on the year of diagnosis, facilitating use of possibly more sensitive survival models.

Future work: Handling misalignment

- So far we have ignored spatial misalignment (Zhu et al., *Environmetrics*, 2003) in our data: the UV observations are really the result of a weather-informed model that collects data at a point level but produces grid level exposure estimates, which we assume apply to every resident of the grid
- There is also a form of temporal misalignment: the most relevant (e.g., childhood) UV exposures may vary both spatially and temporally, yet we currently ignore the latter

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- There is also a form of temporal misalignment: the most relevant (e.g., childhood) UV exposures may vary both spatially and temporally, yet we currently ignore the latter
- Fuentes et al. (*Biometrics*, 2006) give a generalized Poisson model for areal mortality counts $Y_{jk}(t)$ over strata (e.g., gender, age, etc.) k and counties j by month t
  - Covariates in the log-link include county-level confounders (e.g., ozone) $\mathbf{U}_j(t)$, strata-level confounders (e.g., gender, age, etc.) $\mathbf{X}_k(t)$, and I different PM exposure species $\mathbf{V}_j(t)$.
  - The spatial misalignment is resolved by integrating an underlying "total" PM surface $Z(s,t)$ over the counties C_j, where this is in turn modeled linearly as a function of weather variables $W(s,t)$.

Fuentes et al. (2006) model

For month t, county j, and stratum k,

$$
\begin{aligned}
Y_{jk}(t) &\sim GPoi(\alpha, \mu_{jk}(t)) \\
log(\mu_{jk}(t)) &= \mathbf{U}_j^T(t)\gamma_1 + \mathbf{X}_k^T(t)\gamma_2 + \mathbf{V}_j^T(t)\beta, \\
\text{where} \quad & \mathbf{V}_j^T(t) = (V_{1j}(t), \ldots, V_{Ij}(t)) \\
V_{ij}(t) &= \xi_i(t) \int_{C_j} Z(s,t)ds + \phi_{ij}(t) \\
\phi_j(t)|\phi_{-j}(t) &\sim N\left(\sum_{j' \neq j} B_{jj'}(t)\phi_{j'}(t), \frac{1}{m_j}\Sigma_\phi(t)\right), \\
\text{where} \quad & \phi_j(t)^T = (\phi_{1j}(t), \ldots, \phi_{Ij}(t)) \\
Z(s,t) &= \mathbf{W}^T(s,t)\boldsymbol{\eta} + \epsilon(s,t)
\end{aligned}
$$

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Y_{jk}(t) &\sim GPoi(\alpha, \mu_{jk}(t)) \\
log(\mu_{jk}(t)) &= \mathbf{U}_j^T(t)\gamma_1 + \mathbf{X}_k^T(t)\gamma_2 + \mathbf{V}_j^T(t)\boldsymbol{\beta}, \\
\text{where} \quad & \mathbf{V}_j^T(t) = (V_{1j}(t), \ldots, V_{Ij}(t)) \\
V_{ij}(t) &= \xi_i(t) \int_{C_j} Z(s,t)ds + \phi_{ij}(t) \\
\phi_j(t)|\phi_{-j}(t) &\sim N\left(\sum_{j' \neq j} B_{jj'}(t)\phi_{j'}(t), \frac{1}{m_j}\Sigma_\phi(t)\right), \\
\text{where} \quad & \phi_j(t)^T = (\phi_{1j}(t), \ldots, \phi_{Ij}(t)) \\
Z(s,t) &= \mathbf{W}^T(s,t)\boldsymbol{\eta} + \epsilon(s,t)
\end{aligned}
$$

- Here, $\xi_i(t)$ represents the proportion of total exposure at time t explained by PM species i
- a multivariate CAR (MCAR) model for the $\phi_{ij}(t)$ allows covariance structure $\Sigma_\phi(t)$ that evolves over time

Future Work: Gaussian Process model

Returning to our setting and again thinking of time within summer t as continuous, modify our UV model for grid i to

$$Y_i(t) = \mu_i(t) + \epsilon_i(t) \ ,$$

where the $\epsilon_i(t)$ are from a white noise process, and

$$\mu_i(t) = \mu_0 + \gamma_{0i} + \alpha W_{2i} + Z_i(t) \ .$$

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Writing

$$\mathbf{Z} = (\mathbf{Z}'(t_1), \ldots, \mathbf{Z}'(t_T))',$$

where

$$\mathbf{Z}(t) = (Z_1(t), \ldots, Z_{81}(t))'$$

for any t, assume the $Z_i(t)$ follow a spatial Gaussian process (GP) model...

Future Work: Gaussian Process model

Specifically, model $\mathbf{Z} \sim N(\mathbf{0}, \boldsymbol{\Sigma})$ where

$$\boldsymbol{\Sigma} = R(\phi) \otimes \tau^2 (D - \lambda W)^{-1} ,$$

the Kronecker product of

- $T \times T$ temporal correlation matrix $R(\phi)$ (say, (t_1, t_2) element $\exp(-\phi|t_1 - t_2|)$), and
- $M \times M$ spatial correlation matrix (say, of the usual CAR type)
  - Adjacency matrix W, with $w_{ii'} = I(i' \in \partial_i)$, where ∂_i is the neighbor set of i
  - D is diagonal with $D_{ii} = w_{i+}$
  - Smoothing parameter $\lambda \in (0, 1)$

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  - D is diagonal with $D_{ii} = w_{i+}$
  - Smoothing parameter $\lambda \in (0, 1)$
- We are interested in the temporal gradient, $Z_i'(t)$:
  - We seek the t where this becomes significantly > 0
  - May vary both temporally (function of t) and spatially (for each i)

Final thoughts on the spatial GP model

- Note that while the derivative process is never observed, inference may still proceed from the predictive distribution, $P(Z_i'(t_0)|\mathbf{Z})$
- Possible to compute because:
  - covariance functions yield mean square differentiable paths, and
  - sampling from the posterior predictive easy via composition (Gaussian kernel with the Gibbs posterior draws)

Final thoughts on the spatial GP model

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- Possible to compute because:
  - covariance functions yield mean square differentiable paths, and
  - sampling from the posterior predictive easy via composition (Gaussian kernel with the Gibbs posterior draws)
- Potentially important in our IR/UV/NMSC setting since if UV exposure is increasing over time, identical self-reports of exposure from widely different years may correspond to quite different cancer risks!
- Ideally, all of this structure would be added to our logistic model for the NMSC responses, now indexed by both individual k and exposure epoch t.

THE END (for now)