Hierarchical multivariate directed acyclic graph autoregressive models for spatial diseases mapping

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Abstract
Disease mapping is an important statistical tool used by epidemiologists to assess geographic variation in disease rates and identify lurking environmental risk factors from spatial patterns. Such maps rely upon spatial models for regionally aggregated data, where neighboring regions tend to exhibit similar outcomes than those farther apart. We contribute to the literature on multivariate disease mapping, which deals with measurements on multiple (two or more) diseases in each region. We aim to disentangle associations among the multiple diseases from spatial autocorrelation in each disease. We develop multivariate directed acyclic graphical autoregression models to accommodate spatial and inter-disease dependence. The hierarchical construction imparts flexibility and richness, interpretability of spatial autocorrelation and inter-disease relationships, and computational ease, but depends upon the order in which the cancers are modeled. To obviate this, we demonstrate how Bayesian model selection and averaging across orders are easily achieved using bridge sampling. We compare our method with a competitor using simulation studies and present an application to multiple cancer mapping using data from the Surveillance, Epidemiology, and End Results program.

KEYWORDS
areal data analysis, Bayesian hierarchical models, directed acyclic graphical autoregression, multiple disease mapping, multivariate areal data models

1 | INTRODUCTION

Spatially referenced data comprising regional aggregates of health outcomes over delineated administrative units such as counties or zip codes are widely used by epidemiologists to map mortality or morbidity rates and better understand their geographic variation. Disease mapping, as this exercise is customarily called, employs statistical models to present smoothed maps of rates or counts of a disease. Such maps can assist investigators in identifying lurking risk factors1 and in detecting “hot-spots” or spatial clusters emerging from common environmental and socio-demographic effects shared by neighboring regions. By interpolating estimates of health outcome from areal data onto a continuous surface, disease mapping also generates smoothed maps for the small-area scale, adjusting for the sparsity of data or low population size.2,3

For a single disease, there has been a long tradition of employing Markov random fields (MRFs)4 to introduce conditional dependence for the outcome in a region given its neighbors. Two conspicuous examples are the conditional
autoregression (CAR)\textsuperscript{5,6} and simultaneous autoregression (SAR) models\textsuperscript{7} that build dependence using undirected graphs to model geographic maps. More recently, a class of directed acyclic graphical autoregressive (DAGAR) models was proposed as a preferred alternative to CAR or SAR models in allowing better identifiability and interpretation of spatial autocorrelation parameters.\textsuperscript{8}

Multivariate disease mapping is concerned with the analysis of multiple diseases that are associated among themselves and across space. It is not uncommon to find substantial associations among different diseases sharing genetic and environmental risk factors. Quantification of genetic correlations among multiple cancers has revealed associations among several cancers including lung, breast, colorectal, ovarian, and pancreatic cancers.\textsuperscript{9} Disease mapping exercises with lung and esophageal cancers have also evinced associations among them.\textsuperscript{10} When the diseases are inherently related so that the prevalence of one encourages (or inhibits) occurrence of the other, there can be substantial inferential benefits in jointly modeling the diseases rather than fitting independent univariate models for each disease.\textsuperscript{10-21}

The existence of multivariate MRFs can be demonstrated using a multivariate extension of the so called “Brook’s lemma,” which attempts to derive a joint distribution from specified full conditionals.\textsuperscript{13,22,23} McNab, in a series of papers, has delivered substantial insights into the construction, computation, and properties of different classes of multivariate CAR models.\textsuperscript{21,24-26} Rather than work with full conditionals, an alternate approach builds joint distributions using linear transformations of a set of univariate CAR models.\textsuperscript{14,16,19,27,28} A different class emerges from hierarchical constructions\textsuperscript{10,29} where each disease enters the model in a given sequence (or order) of conditional probability models. This produces simple yet flexible and interpretable association structures, but every ordering produces a different model resulting in an explosion of models even for a modest number of cancers (say, more than 2 or 3 diseases). While multivariate MRF models constructed from undirected graphs are invariant to ordering, hence obviate the issue of order dependence, they impose restrictions to ensure positive-definiteness of covariance matrices, can be computationally onerous and render covariance structures that are challenging to interpret.

We introduce a class of multivariate DAGAR (MDAGAR) models for multiple diseases mapping by building the joint distribution hierarchically using univariate DAGAR models. This approach is analogous to generalized MCAR (GMCAR) models.\textsuperscript{10} The objective here is to retain the interpretation of spatial autocorrelation offered by the DAGAR, which is challenging for the CAR\textsuperscript{30} and order-free MCAR models. Our methodological innovation is devising a hierarchical MDAGAR model in conjunction with a bridge sampling algorithm\textsuperscript{31,32} for choosing among differently ordered hierarchical models and, more importantly, offering Bayesian model averaged (BMA) inference to neutralize the effect of order dependent inference. The idea is to begin with a fixed ordered set of cancers, posited to be associated with each other and across space, and build a hierarchical model. The DAGAR specification produces a comprehensible association structure, while bridge sampling allows us to rank differently ordered models using their marginal posterior probabilities. Since each model corresponds to an assumed conditional dependence, the marginal posterior probabilities will indicate the tenability of such assumptions given the data. Epidemiologists, then, will be able to use this information to establish relationships among the diseases and spatial autocorrelation for each disease.

The article proceeds as follows. Section 2 develops the hierarchical MDAGAR model and introduces a bridge sampling method to select the MDAGAR with the best hierarchical order. Section 3 presents simulation studies comparing MDAGAR with GMCAR and order-free MCAR models and also illustrates model averaged inference from the bridge sampling. Section 4 applies our MDAGAR to age-adjusted incidence rates of four cancers from the Surveillance, Epidemiology, and End Results (SEER) database and discusses different cases with respect to predictors. Finally, in Section 5, we summarize with some concluding remarks and pointers for future research.

## 2  METHODS

### 2.1  Overview of univariate DAGAR modeling

Let $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ be a graph corresponding to a geographic map, where the vertices $\mathcal{V} = \{1, 2, \ldots, k\}$ represent clearly delineated regions on the map and $\mathcal{E} = \{(i,j) : i \sim j\}$ is the collection of edges between the vertices representing neighboring pairs of regions. We denote two neighboring regions $i$ and $j$ by $i \sim j$. We assume that the vertices in $\mathcal{V}$ are ordered in a fixed sequence according to their number labels. The DAGAR model builds a spatial autocorrelation model for a single outcome on $\mathcal{G}$ using the ordered set of vertices in $\mathcal{V}$.\textsuperscript{8} Let $N(1)$ be the empty set and let $j \in \mathcal{V} \setminus \{1\}$ be the index for any region except 1. We define $N(j)$ to be the set of labels of geographic neighbors of $j$ that precede $j$ in $\mathcal{V}$, that is, $N(j) = \{l \in \mathcal{V} : l < j ; \ l \sim j\}$.\textsuperscript{8} Let $\mathcal{W}_i : i \in \mathcal{V}$ be a collection of $k$ random variables defined over the map. DAGAR
motivating multivariate disease mapping

\[ w_1 = \epsilon_1; \quad w_j = \sum_{i\in N(j)} b_{jl} w_l + \epsilon_j, \quad j = 2, \ldots, k, \quad (1) \]

where \( \epsilon_i \sim N(0, \lambda_i) \) with the precision \( \lambda_i \), and \( b_{jl} = 0 \) if \( l \not\in N(j) \). This implies that \( w \sim N(0, rQ(\rho)) \), where \( Q(\rho) \) is a spatial precision matrix that depends only upon a spatial autocorrelation parameter \( \rho \) and \( r \) is a positive scale parameter. The precision matrix \( Q(\rho) = (I - B)^T F(I - B) \), \( B \) is a \( k \times k \) strictly lower-triangular matrix and \( F \) is a \( k \times k \) diagonal matrix. The elements of \( B \) and \( F \) are denoted by \( b_{jl} \) and \( \lambda_j \), respectively, where

\[
b_{jl} = \begin{cases} 0, & \text{if } l \not\in N(j) \\ \frac{\rho}{1+(n_{cj}-1)\rho}, & \text{if } j = 2, 3, \ldots, k, l \in N(j) \end{cases} \quad \text{and} \quad \lambda_j = \frac{1 + (n_{cj} - 1) \rho^2}{1 - \rho^2}, \quad j = 1, 2, \ldots, k. \quad (2)\]

\( n_{cj} \) is the number of members in \( N(j) \) and \( n_{cB} = 0 \). The above definition of \( b_{jl} \) is consistent with the lower-triangular structure of \( cB \) because \( l \not\in N(j) \) for any \( l \geq j \). The derivation of \( B \) and \( F \) as functions of a spatial correlation parameter \( \rho \) is based upon forming local autoregressive models on embedded spanning trees of subgraphs of \( G \).

DAGAR and CAR are both examples of MRFs. They are similar in that both models use a graph to model geographic neighbors, but they are different in how they model spatial dependencies. DAGAR, as the name suggests, builds dependencies using a directed acyclic graph (DAG). This produces a joint likelihood using sequential construction of the partial conditional distributions \( w_l \mid w_{<l} \). CAR builds a joint model by specifying Gaussian full conditional distributions \( w_l \mid w_{<l} \) by treating the underlying map as an undirected graph, where absence of an edge between two regions denotes conditional independence of their spatial effects given other geographic neighbors. These two approaches yield different structures for the precision matrix \( Q(\rho) \) with different interpretations for the parameter \( \rho \). DAGAR retains the interpretation of \( \rho \) as an autocorrelation parameter, \( ^{8} \) while the interpreting spatial autocorrelation in CAR is challenging. \(^{30} \)

\[2.2 \quad \text{Motivating multivariate disease mapping}\]

There is a substantial literature on joint modeling of multiple spatially oriented outcomes, some of which have been cited in Section 1. While it is possible to model each disease separately using a univariate DAGAR, hence independent of each other, the resulting inference will ignore the association among the diseases. This will be manifested in model assessment because the less dependence among diseases that a model accommodates, the farther away it will be from the joint model in the sense of Kullback-Leibler divergence.

More formally, suppose we have two mutually exclusive sets \( A \) and \( B \) that contain labels for diseases. Let \( y_A \) and \( y_B \) be the vectors of spatial outcomes over all regions corresponding to the diseases in set \( A \) and set \( B \), respectively. A full joint model \( p(y) \), where \( y = (y_A^T, y_B^T)^T \), can be written as \( p(y) = p(y_A) \times p(y_B \mid y_A) \). Let \( C_1 \) and \( C_2 \) be two nested subsets of diseases in \( A \) such that \( C_2 \subset C_1 \subset A \). Consider two competing models, \( p_1(y) = p(y_A) \times p(y_B \mid y_{C_1}) \) and \( p_2(y) = p(y_A) \times p(y_B \mid y_{C_2}) \), where \( p_1(\cdot) \) and \( p_2(\cdot) \) are probability densities constructed from the joint probability measure \( p(\cdot) \) by imposing conditional independence such that \( p(y_B \mid y_A) = p(y_B \mid y_{C_1}) \) and \( p(y_B \mid y_A) = p(y_B \mid y_{C_2}) \), respectively. Both \( p_1(\cdot) \) and \( p_2(\cdot) \) suppress dependence by shrinking the conditional set, \( A \), but \( p_2(\cdot) \) suppresses more than \( p_1(\cdot) \). We show below that \( p_2(\cdot) \) is farther away from \( p(\cdot) \) than \( p_1(\cdot) \).

A straightforward application of Jensen’s inequality yields \( E_{B \mid C_1} \left[ \log \frac{p(y_B \mid y_{C_1})}{p(y_B \mid y_{C_2})} \right] \geq 0 \), where \( E_{B \mid C_1} [\cdot] \) denotes the conditional expectation with respect to \( p(y_B \mid y_{C_1}) \). Therefore,

\[
\begin{align*}
\text{KL}(p \parallel p_2) - \text{KL}(p \parallel p_1) &= E_{A,B} \left[ \log \left( \frac{p(y)}{p_2(y)} \right) - \log \left( \frac{p(y)}{p_1(y)} \right) \right] = E_{A,B} \left[ \log \frac{p_1(y)}{p_2(y)} \right] = E_{A,B} \left[ \log \frac{p(y_B \mid y_{C_1})}{p(y_B \mid y_{C_2})} \right] \\
&= E_{B,C_1} \left[ \log \frac{p(y_B \mid y_{C_1})}{p(y_B \mid y_{C_2})} \right] = E_{C_1} \left[ E_{B \mid C_1} \left[ \log \frac{p(y_B \mid y_{C_1})}{p(y_B \mid y_{C_2})} \right] \right] \geq 0. \quad (3)
\end{align*}
\]
The equality \( E_{AB}[-] = E_{BC}[-] \) in the last row follows from the fact that the argument is a function of diseases in \( B, C_1 \) and \( C_2 \) and, hence, in \( B \) and \( C_1 \) because \( C_2 \subseteq C_1 \). The argument given in (3) is free of distributional assumptions and is linked to the submodularity of entropy and the “information never hurts” principle.\(^{33,34}\) Equation (3) shows that models built upon hierarchical dependence structures depend upon the order in which the diseases enter the model. While this is a disadvantage, hierarchical dependencies are easier to interpret, easier to compute using currently available Bayesian modeling software such as BUGS or JAGS and have been shown to be very competitive in inferential performance.\(^{35}\) Hence, we develop and implement Bayesian model averaging over different ordered models in a computationally efficient manner.

### 2.3 Multivariate DAGAR model

Modeling multiple diseases will introduce associations among the diseases and spatial dependence for each disease. Let \( y_{ij} \) be a disease outcome of interest for disease \( i \) in region \( j \). For sake of clarity, we assume that \( y_{ij} \) is a continuous variable (e.g., incidence rates) related to a set of explanatory variables through the regression model,

\[
y_{ij} = x_{ij}' \beta_i + w_{ij} + e_{ij},
\]

where \( x_{ij} \) is a \( p_i \times 1 \) vector of explanatory variables specific to disease \( i \) within region \( j \), \( \beta_i \) are the slopes corresponding to disease \( i \), \( w_{ij} \) is a random effect for disease \( i \) in region \( j \), and \( e_{ij} \sim N(0, (\sigma_i^2)^{-1}) \) is the random noise arising from uncontrolled imperfections in the data.

Part of the residual from the explanatory variables is captured by the spatial-temporal effect \( w_{ij} \). Let \( w_i = (w_{i1}, w_{i2}, \ldots, w_{iq})' \) for \( i = 1, 2, \ldots, q \). We adopt a hierarchical approach,\(^{10}\) where we specify the joint distribution of \( w = (w_1', w_2', \ldots, w_q')' \) as \( p(w) = p(w_1) \prod_{i=2}^q p(w_i | w_{ci}) \). We model \( p(w_1) \) and each of the conditional densities \( p(w_i | w_{ci}) \) with \( w_{ci} = (w_{i1}', \ldots, w_{i(q-1)}')' \) for \( i \geq 2 \) as univariate spatial models. The merits of this approach include simplicity and computational efficiency while ensuring that richness in structure is accommodated through the \( p(w_i | w_{ci}) \)'s.

We point out two important distinctions from the GMCAR model\(^{10}\): (i) instead of using CAR for the spatial dependence, we use DAGAR; and (ii) we apply a computationally efficient bridge sampling algorithms\(^{32}\) to compute the marginal posterior probabilities for each ordered model. The first distinction allows better interpretation of spatial autocorrelation than the CAR models. The second distinction is of immense practical value and makes this approach feasible for a much larger number of outcomes. Without this distinction, analysts would be dealing with \( q! \) models for \( q \) diseases and choose among them based upon a model-selection metric. That would be overly burdensome for more than 2 or 3 diseases.

### 2.4 A conditional multivariate DAGAR model

The multivariate DAGAR (or MDAGAR) model is constructed as

\[
w_i = e_i; \quad w_i = A_i w_1 + A_{i2} w_2 + \cdots + A_{i,i-1} w_{i-1} + e_i \text{ for } i = 2, 3, \ldots, q,
\]

where \( e_i \sim N(0, \tau_i Q(\rho_i)) \) and \( \tau_i Q(\rho_i) \) are univariate DAGAR precision matrices with \( B \) and \( F \) as in (2). In (5), we model \( w_i \) as a univariate DAGAR and, progressively, the conditional density of each \( w_i \) given \( w_1, \ldots, w_{i-1} \) is also as a DAGAR for \( i = 2, 3, \ldots, q \).

Each disease has its own distribution with its own spatial autocorrelation parameter. There are \( q \) spatial autocorrelation parameters, \( \{ \rho_1, \rho_2, \ldots, \rho_q \} \), corresponding to the \( q \) diseases. Given the differences in the geographic variation of different diseases, this flexibility is desirable. Each matrix \( A_{ii'} \) in (5) with \( i' = 1, \ldots, i-1 \) models the association between diseases \( i \) and \( i' \). We specify \( A_{ii'} = \eta_{ii'} I_k + \eta_{iii'} M \), where \( M \) is the binary adjacency matrix for the map, that is, \( m_{jj'} = 1 \) if \( j' \sim j \) and 0 otherwise. Coefficients \( \eta_{ii'} \) and \( \eta_{iii'} \) associate \( w_{ij} \) with \( w_{ij} \) and \( w_{ij} \). In other words, \( \eta_{ii'} \) is the diagonal element in \( A_{ii'} \), while \( \eta_{ii'} \) is the element in the \( j \)th row and \( j' \)th column if \( j' \sim j \). Therefore, for the joint distribution of \( w_i \), if \( A \) is the \( kq \times kq \) strictly block-lower triangular matrix with \((ii')\)th block being \( A_{ii'} = O \) whenever \( i' \geq i \) and \( e = (e_1, \ldots, e_q)' \), then (5) renders \( w = A w + e \).
Since $I - A$ is still lower triangular with 1s on the diagonal, it is nonsingular with $\det(I - A) = 1$. Writing $w = (I - A)^{-1}c$, where $c \sim N(0, \Lambda)$ and the block diagonal matrix $\Lambda$ has $\tau_1 Q(\rho_1), \ldots, \tau_q Q(\rho_q)$ on the diagonal, we obtain $w \sim N(0, Q_w)$ for $\rho = (\rho_1, \ldots, \rho_q)^T$ with

$$Q_w = (I - A)^T \Lambda (I - A).$$

We say that $w$ follows MDAGAR if $w \sim N(0, Q_w)$.

Interpretation of $\rho_1, \ldots, \rho_q$ is clear: $\rho_1$ measures the spatial association for the first disease, while $\rho_i$, $i \geq 2$, is the residual spatial correlation in the disease $i$ after accounting for the first $i - 1$ diseases. Similarly, $\tau_1$ is the spatial precision for the first disease, while $\tau_i$, $i \geq 2$, is the residual spatial precision for disease $i$ after accounting for the first $i - 1$ diseases.

2.4.1 Model implementation

We extend (4) to the following Bayesian hierarchical framework with the posterior distribution

$$p(\beta, w, \eta, \rho, \tau, \sigma | y) \propto p(\rho) \times p(\eta) \times \prod_{i=1}^{q} \left\{ IG(1/\tau_i | a_\tau, b_\tau) \times IG(\sigma_i^2 | a_\sigma, b_\sigma) \times N(\beta_i | \mu_\beta, V_\beta^{-1}) \right\} \times N(w | 0, Q_w) \times \prod_{i=1}^{q} \prod_{j=1}^{k} N(y_{ij} | x_{ij}^T \beta_i + w_{ij}, 1/\sigma_i^2),$$

(7)

where $\beta = (\beta_1^T, \beta_2^T, \ldots, \beta_q^T)^T$, $\tau = (\tau_1, \tau_2, \ldots, \tau_q)$, $\sigma = (\sigma_1^2, \sigma_2^2, \ldots, \sigma_q^2)$, and $\eta = (\eta_1, \eta_2, \ldots, \eta_q)$ with $\eta_i = (\eta_{i1}^T, \eta_{i2}^T, \ldots, \eta_{i(i-1)}^T)$ and $\eta_{ij} = (\eta_{ij1}, \eta_{ij2})^T$ for $i = 2, \ldots, q$ and $j = 1, \ldots, i - 1$. For variance parameters $1/\tau_i$ and $\sigma_i^2$, $IG(\cdot | a, b)$ is the inverse-gamma distribution with shape and rate parameters $a$ and $b$, respectively. For each element in $\eta_i$ we choose a normal prior $N(\mu_{ij}, \sigma_{ij}^2)$, while the prior $N(w | 0, Q_w)$ can also be written as

$$p(w | \tau, \eta_2, \ldots, \eta_q, \rho) \propto r_1^{\frac{1}{2}} |Q(\rho_1)|^{\frac{1}{2}} \exp \left\{ -\frac{r_1}{2} w_1^T Q(\rho_1) w_1 \right\} \times \prod_{i=2}^{q} r_i^{\frac{1}{2}} |Q(\rho_i)|^{\frac{1}{2}} \exp \left\{ -\frac{r_i}{2} w_i^T \left( w_i - \sum_{j=1}^{i-1} \mathcal{A}_{ij} w_j \right) \right\}^T Q(\rho_i) \left( w_i - \sum_{j=1}^{i-1} \mathcal{A}_{ij} w_j \right),$$

(8)

where $\det(Q(\rho_i)) = \prod_{j=1}^{k} \lambda_{ij}$, and $w_i^T Q(\rho_i) w_i = \lambda_{i1} w_{i1}^2 + \sum_{j=2}^{k} \lambda_{ij} (w_{ij} - \sum_{j'=N(i)} b_{ij'} w_{ij'})^2$.

We sample the parameters from the posterior distribution in (7) using Markov chain Monte Carlo (MCMC) with Gibbs sampling and random walk metropolis as implemented in the rjags package within the R statistical computing environment. Web Appendix B S.2.1 presents details on the MCMC updating scheme.

2.5 Model selection via bridge sampling

It is clear from (5) that each ordering of diseases in MDAGAR will produce a different model. For the bivariate situation, it is convenient to compare only two models (orders) by the significance of parameter estimates as well as model performance. However, when there are more than two diseases involved in the model, at least six models (for three diseases) will be fitted and comparing all models become cumbersome or even impracticable.

Instead, we pursue model averaging of MDAGAR models. Given a set of $T = q!$ candidate models, say $M_1, \ldots, M_T$, Bayesian model selection and model averaging calculates

$$p(M = M_t | y) = \frac{p(y | M = M_t) p(M = M_t)}{\sum_{j=1}^{T} p(y | M = M_j) p(M = M_j)},$$

(9)

for $t = 1, \ldots, T$. Computing the marginal likelihood $p(y | M_t)$ in (9) is challenging. Methods such as importance sampling and generalized harmonic mean have been proposed as stable estimators with finite variance, but finding the required importance density with strong constraints on the tail behavior relative to the posterior distribution is often
challenging. Bridge sampling estimates the marginal likelihood (ie, the normalizing constant) by combining samples from two distributions: a bridge function \( h(\cdot) \) and a proposal distribution \( g(\cdot) \). Let \( \theta_i = \{ \beta_i, \sigma_i, \tau_i, \eta_{1,i}, \ldots, \eta_{q,i} \} \) be the set of parameters in model \( M_i \) with prior \( p(\theta_i | M_i) \) as defined in the first row of (7). Based on the identity,

\[
1 = \frac{\int p(\mathbf{y} | \theta_i, M_i)p(\theta_i | M_i)h(\theta_i | M_i)g(\theta_i | M_i)d\theta_i}{\int p(\mathbf{y} | \theta_i, M_i)p(\theta_i | M_i)h(\theta_i | M_i)g(\theta_i | M_i)d\theta_i},
\]

a current version of the bridge sampling estimator is

\[
p(\mathbf{y} | M_i) = \frac{\int p(\mathbf{y} | \theta_i, M_i)p(\theta_i | M_i)h(\theta_i | M_i)g(\theta_i | M_i)d\theta_i}{\int p(\mathbf{y} | \theta_i, M_i)p(\theta_i | M_i)h(\theta_i | M_i)g(\theta_i | M_i)d\theta_i} \\
\approx \frac{\frac{1}{N} \sum_{i=1}^{N_i} p(\mathbf{y} | \bar{\theta}_{i,1}, M_i)p(\bar{\theta}_{i,1} | M_i)h(\bar{\theta}_{i,1} | M_i)}{\frac{1}{N} \sum_{j=1}^{N_i} p(\theta^*_{i,j} | M_i)g(\theta^*_{i,j} | M_i)},
\]

where \( \theta^*_{i,j} \sim p(\theta_i | M_i) \) is a set of \( N_i \) posterior samples and \( \bar{\theta}_{i,1} \sim g(\theta_i | M_i) \) are \( N_i \) samples drawn from the proposal distribution. The likelihood \( p(\mathbf{y} | \theta_i, M_i) \) is obtained by integrating out \( \mathbf{w} \) from (7) as

\[
N(\mathbf{y} | \mathbf{X} \beta, [Q_w^{-1} (\rho_i, \tau_i, \eta_{1,i}, \ldots, \eta_{q,i}) + \text{diag}(\sigma_i) \otimes I_k]^{-1}),
\]

given that \( \mathbf{y} = (\mathbf{y}_1^T, \ldots, \mathbf{y}_T^T)^T \) with \( \mathbf{y}_i = (y_{i1}, y_{i2}, \ldots, y_{ik})^T \), \( \text{diag}(\sigma) \) is a diagonal matrix with \( \sigma_i^2, i = 1, \ldots, q \), on the diagonal, and \( \mathbf{X} \) is the design matrix with \( \mathbf{X}_i \) as block diagonal where \( \mathbf{X}_i = (\mathbf{x}_{i1}, \mathbf{x}_{i2}, \ldots, \mathbf{x}_{ik})^T \). The bridge function \( h(\theta_i | M_i) \) is specified by the optimal choice as

\[
h(\theta_i | M_i) = C \frac{1}{\sum_{i=1}^{N_i} \sum_{j=1}^{l_{ij}} p(\theta_{i,j}^* | M_i)g(\theta_{i,j}^* | M_i)}
\]

where \( C \) is a constant. Inserting (12) in (10) yields the estimate of \( p(\mathbf{y} | M = M_i) \) after convergence of an iterative scheme as

\[
\hat{p}(\mathbf{y} | M_i)^{(t+1)} = \frac{\frac{1}{N} \sum_{j=1}^{N_i} \sum_{i=1}^{l_{ij}} f(\theta_{i,j}^* | M_i)}{\frac{1}{N} \sum_{j=1}^{N_i} \sum_{i=1}^{l_{ij}} f(\theta_{i,j}^* | M_i)}
\]

where \( l_{ij} = \frac{p(\mathbf{y} | \theta_{i,j}^* | M_i)p(\theta_{i,j}^* | M_i)}{g(\theta_{i,j}^* | M_i)}, l_{2i} = \frac{p(\mathbf{y} | \bar{\theta}_{i,1} | M_i)p(\bar{\theta}_{i,1} | M_i)}{g(\bar{\theta}_{i,1} | M_i)}, s_1 = \frac{N_i}{N_i + N^2}, \) and \( s_2 = \frac{N^2}{N_i + N^2} \).

Given the log marginal likelihood estimates from bridge sampling, the posterior model probability for each model is calculated from (9) by setting prior probability of each model \( p(M = M_i) \). For Bayesian model averaging (BMA), the model averaged posterior distribution of a quantity of interest \( \Delta \) is obtained as \( p(\Delta | \mathbf{y}) = \sum_{i=1}^{I} p(\Delta | M = M_i, \mathbf{y})p(M = M_i | \mathbf{y}) \), and the posterior mean is

\[
E(\Delta | \mathbf{y}) = \sum_{i=1}^{I} E(\Delta | M = M_i, \mathbf{y})p(M = M_i | \mathbf{y})
\]

Setting \( \Delta = \{ \beta, \mathbf{w} \} \) fetches us the model averaged posterior estimates for spatial random effects as well as calculating the posterior mean incidence rates as discussed in Section 4.

### 3 Simulation

We simulate three different experiments. The first is designed to evaluate MDAGAR’s inferential performance against GMCAR. The second compares MDAGAR, GMCAR and order-free MCAR for data generated from the latter. The third experiment illustrates the effectiveness of bridge sampling (Section 2.5) in preferring models with a correct “ordering” of the diseases.
3.1 Data generation

We compare MDAGAR’s inferential performance with GMCAR\(^\text{10}\) (Section 3.2) and order-free MCAR\(^\text{16}\) (Section 3.3). We choose the 48 states of the contiguous United States as our underlying map, where two states are treated as neighbors if they share a common geographic boundary. We generated our outcomes \(y_{ij}\) using the model in (4) with \(q = 2\), that is, two outcomes, and two covariates, \(x_{ij}\) and \(x_{2j}\), with \(p_1 = 2\) and \(p_2 = 3\). We fixed the values of the covariates after generating them from \(N(\mathbf{0}, \mathbf{I}_p)\), \(i = 1, 2\), independent across regions. The regression slopes were set to \(\beta_1 = (1, 5)\)\(^\top\) and \(\beta_2 = (2, 4, 5)\)\(^\top\).

Turning to the spatial random effects, we generated values of \(w = (w_1, w_2)\)\(^\top\) from a \(N(\mathbf{0}, \mathbf{Q}_w)\) distribution, where the precision matrix is

\[
Q_w = \begin{bmatrix}
   r_1Q(\rho_1) + r_2A_{21}Q(\rho_2)A_{21} & r_2A_{21}Q(\rho_2) \\
   r_2Q(\rho_2)A_{21} & r_2Q(\rho_2)
\end{bmatrix}
\]

(15)

We set \(r_1 = r_2 = 0.25\), \(\rho_1 = 0.2\), and \(\rho_2 = 0.8\) in (15) and take \(Q(\rho_i) = D(\rho_i)^{-1}\), where \(D(\rho_i) = \exp(-\phi_i d(i,j',j))\), \(\phi_i = -\log(\rho_i)\) is the spatial decay for disease \(i\) and \(d(i,j',j)\) refers to the distance between the embedding of the \(j\)th and \(j'\)th vertex. The vertices are embedded on the Euclidean plane and the centroid of each state is used to create the distance matrix. Using this exponential covariance matrix to generate the data offers a “neutral” ground to compare the performance of MDAGAR with GMCAR. We specified \(A_{12}\) using fixed values of \(\eta = (\eta_{021}, \eta_{121})\). Here, we considered three sets of values for \(\eta\) to correspond to low, medium and high correlation among diseases. We fixed \(\eta = (0.05, 0.1)\) to ensure an average correlation of 0.15 (range 0.072-0.31); \(\eta = (0.5, 0.3)\) with an average correlation of 0.55 (range 0.45-0.74); and \(\eta = (2.5, 0.5)\) with a mean correlation of 0.89 (range 0.84-0.94). We generated \(w_{ij}\)’s for each of the above specifications for \(\eta\) and, with the values of \(w_{ij}\) generated as above, we generated the outcome \(y_{ij} \sim N(x_i^\top \beta_i + w_{ij}, 1/\sigma_i^2)\), where \(\sigma_1^2 = \sigma_2^2 = 0.4\). We repeat the above procedure to replicate 85 datasets for each of the three specifications of \(\eta\).

For our third experiment (Sections 3.4 and 3.5), we generate a dataset with \(q = 3\) cancers. We extend the above setup to include one more disease. We generate \(y_{ij}\)’s from (4) with the value of \(x_{ij}\) fixed after being generated from \(N(\mathbf{0}, \mathbf{I}_3)\), \(\beta_3 = (5, 3, 6)\)\(^\top\), and \(\sigma_3^2 = 0.4\). Let \([i,j,k]\) denote the model \(p(w_i) \times p(w_j | w_i) \times p(w_k | w_j, w_i)\). For three diseases the six resulting models are denoted as \(M_1 = [1, 2, 3], M_2 = [1, 3, 2], M_3 = [2, 1, 3], M_4 = [2, 3, 1], M_5 = [3, 1, 2],\) and \(M_6 = [3, 2, 1]\).

Each of the six models imply a corresponding joint distribution \(w \sim N(\mathbf{0}, \mathbf{Q}_w)\) which is used to generate the \(w_{ij}\)’s. Let the parenthesesized suffix \((i)\) denote the disease in the \(i\)th order. For example, in \(M_2 = [1, 3, 2]\), we write \(w\) in the form of (5) as

\[
w_1 \sim \epsilon_{(1)}, \quad w_2 = A_{(21)}w_1 + \epsilon_{(2)}, \quad w_3 = A_{(31)}w_1 + A_{(32)}w_2 + \epsilon_{(3)},
\]

where \(\epsilon_{(i)} \sim N(\mathbf{0}, \tau_{(i)}Q(\rho_{(i)}))\) with \(Q(\rho_{(i)}) = D(\rho_{(i)})^{-1}\) as in the first experiment, and \(A_{(i'i')} = \eta_{0(i'i')}I + \eta_{1(i'i')}\mathbf{M}\) is the coefficient matrix associating random effects for diseases in the \(i\)th and \(i'\)th order. We set \(\tau_{(1)} = \tau_{(2)} = \tau_{(3)} = 0.25\), \(\rho_{(1)} = 0.2\), \(\rho_{(2)} = 0.8\), \(\rho_{(3)} = 0.5\), \(\eta_{0(21)} = 0.5\), \(\eta_{0(21)} = 0.3\), \(\eta_{0(31)} = 1\), \(\eta_{1(31)} = 0.6\), \(\eta_{0(32)} = 1.5\), and \(\eta_{1(32)} = 0.9\) to completely specify \(Q_w\) for each of the 6 models. For each \(M_i\), we generate 50 datasets by first generating \(w \sim N(\mathbf{0}, \mathbf{Q}_w)\) and then generating \(y_{ij}\)’s from (4) using the above specifications. Details on the algorithms and the computing environments for each model are provided in Section S.2.1.

3.2 Comparisons between MDAGAR and GMCAR

In our first experiment, we analyzed the 85 replicated datasets using (7) with

\[
p(\rho) \times p(\eta) \propto \prod_{i=1}^{q=2} \{ \text{Unif}(\rho_i \mid 0, 1) \} \times N(\eta_{21} \mid \mathbf{0}, 0.01I_2),
\]

(16)

where \(\eta_{21} = (\eta_{021}, \eta_{121})\)\(^\top\) and Unif is the uniform density. Prior specifications are completed by setting \(a_\tau = 2\), \(b_\tau = 8\), \(a_\sigma = 2\), \(b_\sigma = 0.4\), \(\mu_\beta = \mathbf{0}\), \(V_\beta = 1000I\) in (7). The same set of priors was used for both MDAGAR and GMCAR as they have the same number of parameters with similar interpretations. Both models are fast to compute; MDAGAR reported an average running time of 3.87 minutes for each dataset in the bivariate disease analysis, while that for GMCAR was 6.25 minutes.
We compare models using the widely applicable information criterion (WAIC)\cite{waic, waic2} and a model comparison score $D$ based on a balanced loss function for replicated data.\cite{d_score} Both WAIC and $D$ reward goodness of fit and penalize model complexity. Details on how these metrics are computed are provided in Web Appendix B S.2.2. In addition, we also computed the average mean squared error (AMSE) of the spatial random effects estimated from each of the 85 datasets. We found the mean (standard deviation) of the AMSEs to be $1.69\ (0.034)$ from the 85 low-correlation datasets, $1.47\ (0.030)$ from the 85 medium-correlation datasets, and $2.35\ (0.059)$ from the 85 high-correlation datasets. The corresponding numbers for GMCAR were $1.83\ (0.033)$, $1.59\ (0.031)$, and $2.14\ (0.050)$, respectively. The MDAGAR tends to have smaller AMSE for
low and medium correlations, while GMCAR’s AMSE tends to be pronouncedly lower than MDAGAR’s when the correlations are high. We also compute the mean values of WAICs and D scores for each simulated dataset. Figure 1 plots the values of WAICs (A-C) and D scores (D-F) for the 85 datasets corresponding to each of the three correlation settings. Here, MDAGAR outperforms GMCAR in all three correlation settings with respect to both WAICs and D scores. While MDAGAR outperforms GMCAR in overall model fitting scores for most correlation settings, GMCAR can yield better estimates of spatial effects in high correlation settings.

Figure 2 presents scatter plots for the true values (x-axis) of spatial random effects against their posterior estimates (y-axis). To be precise, each panel plots 85 × 48 × 2 = 8160 true values of the elements of the 96 × 1 vector \( \mathbf{w} \) for 85 datasets against their corresponding posterior estimates. We see strong agreements between the true values and their estimates for both MDAGAR and GMCAR. The agreement is more pronounced for the datasets corresponding to medium and high correlations. For the low-correlation datasets, MDAGAR still exhibits strong agreement which is better than GMCAR.

We compute \( D_{KL}(N(\mathbf{0}, Q_{\text{true}})||N(\mathbf{0}, Q_{w})) = \frac{1}{2} \left[ \log \left( \frac{\det Q_{\text{true}}}{\det Q_{w}} \right) + \text{tr}(Q_{w}^{-1}Q_{\text{true}}^{-1}) - qk \right] \), which is the Kullback-Leibler divergence between the model for \( \mathbf{w} \) with the true generative precision matrix (\( Q_{\text{true}} \)) and those with MDAGAR and GMCAR precisions (\( Q_{w} \)). Using the posterior samples in the precision matrix, we evaluate the posterior probability that \( D_{KL}(N(\mathbf{0}, Q_{\text{true}})||N(\mathbf{0}, Q_{\text{MDAGAR}})) \) is smaller than \( D_{KL}(N(\mathbf{0}, Q_{\text{true}})||N(\mathbf{0}, Q_{w})) \). Figure 3 depicts a density plot of these probabilities over the 85 datasets. When correlations are low and medium, the MDAGAR has a mean probability of around 69% to be closer to the true model than the GMCAR, while for high correlations GMCAR excels with an average probability of 72% to be closer to the true model. These findings are consistent with the AMSEs, where GMCAR tended to perform better when correlations were high. Additional comparative diagnostics from MDAGAR and GMCAR, such as coverage probabilities for parameters and correlations between random effects for two diseases in the same state, are presented in Web Appendix B.S.2.2.2.

### 3.3 Comparisons between MDAGAR and order-free MCAR

We also generated data using an order-free MCAR model\(^{16} \) to evaluate MDAGAR and GMCAR when the underlying structure is different from the proposed conditional scheme. For the MCAR model, we specified the joint covariance matrix of \( \mathbf{w} \) as

\[
Q_{w}^{-1} = (A \otimes I_{kq})\Gamma^{-1}(A \otimes I_{kq})^T,
\]

where \( \Sigma = AA^T \) is a \( q \times q \) matrix corresponding to disease dependence, \( A \) is the upper triangular Cholesky decomposition of \( \Sigma \) and \( \Gamma \) is a \( kq \times kq \) block diagonal matrix with \( \Gamma_{ii}^{-1} = \tau_i^2(D - \rho_i W) \) (\( k \times k \) precision matrix for a proper CAR) for each \( i = 1, \ldots, q \). This corresponds to the MCAR generated from \( \mathbf{w} = (A \otimes I)\mathbf{v} \), where \( \mathbf{v} = (v_1, \ldots, v_q)^T \) and \( v_i \sim N(\mathbf{0}, D - \rho_i W) \) for \( i = 1, \ldots, q \), \( D \) is the diagonal matrix with number of neighbors along the diagonal and \( W \) is a binary adjacency matrix.
Therefore, \( w \) is generated from independent but not identically distributed latent proper CAR distributions (see Reference 16, Section 3.2).

Keeping other model specifications same as in Section 3.1 (so \( q = 2 \) and \( \rho_i \)'s are as in Section 3.1), we fixed \( A = \begin{bmatrix} 1 & 0 \\ 0.7 & 1 \end{bmatrix} \). Computing (17) with these specifications yields a mean correlation of 0.52 among the entries of the matrix (range: 0.48-0.54). The above procedure is replicated for 50 datasets for each model. We estimated the MDAGAR and GMCAR models in two opposite orders, denoted MDAGAR1, MDAGAR2, GMCAR1, and GMCAR2, and compared with the order-free MCAR. We estimate (7) with the respective specifications for \( Q_w \) for each model. For the MDAGAR and GMCAR models, we used the priors specified in the previous section using (16). For the MCAR, we assigned \( \log a_{ii} \), \( i = 1, 2, \) and \( a_{21} \) with normal priors with variances 0.0625 and 100, respectively. The order-free MCAR is also fast to compute and reported an average running time of 5.89 minutes for each dataset in this experiment.

Figure 4 plots values of (A) WAICs, (B) \( D \) scores, and (C) the posterior mean of \( D_{KL}(p(y_{\text{true}})||p(y)) \) over 50 datasets, respectively, using MDAGAR1, MDAGAR2, GMCAR1, GMCAR2, and MCAR. The dot vertical line shows the mean for each plot.

Figure 5 plots values of (A) WAICs, (B) \( D \) scores, and (C) the posterior mean of \( D_{KL}(p(y_{\text{true}})||p(y)) \) over 85 datasets for the MDAGAR model using four different orderings: Northeast (red), northwest (green), southeast (blue), and southwest (purple). The dotted vertical line shows the mean for each plot.

3.4 Analyses using different orderings for spatial units

The MDAGAR model in Section 3.2 is analyzed using an ordering of spatial units (counties) from the southwest to the northeast. Here, we repeat the analysis for the MDAGAR model using three other orderings that start in the southeast, northwest, and northeast, respectively. We present results from these differently ordered DAGAR models using the 85
### Table 1
Proportion of times ($\pi(M_i)$) bridge sampling chose the model with the correct order out of the 50 datasets with that order

| True model | $\pi(M_1)$ | $\pi(M_2)$ | $\pi(M_3)$ | $\pi(M_4)$ | $\pi(M_5)$ | $\pi(M_6)$ |
|------------|-----------|-----------|-----------|-----------|-----------|-----------|
| $M_1$      | 0.90      | 0.00      | 0.10      | 0.00      | 0.00      | 0.00      |
| $M_2$      | 0.00      | 0.86      | 0.00      | 0.00      | 0.14      | 0.00      |
| $M_3$      | 0.14      | 0.00      | 0.86      | 0.00      | 0.00      | 0.00      |
| $M_4$      | 0.00      | 0.00      | 0.00      | 0.90      | 0.00      | 0.10      |
| $M_5$      | 0.00      | 0.22      | 0.00      | 0.00      | 0.78      | 0.00      |
| $M_6$      | 0.00      | 0.00      | 0.00      | 0.16      | 0.00      | 0.84      |

---

**Figure 6**
Maps of 5-year average age-adjusted incidence rates per 100,000 population for lung, esophagus, larynx, and colorectal cancer in California, 2012 to 2016.

Low-correlation simulated datasets. For the random effects, the mean (standard deviation) of the AMSEs for three different orderings (southeast, northwest, and northeast) are 1.61 (0.029), 1.28 (0.026), and 1.43 (0.027), respectively, without significantly differing from the original ordering in Section 3.2.

Figure 5 plots the densities of mean WAICs, $D$ scores, and $D_{KL}(p(y_{true}) || p(y))$ over the 85 datasets for the MDAGAR model using three different orderings and the original ordering in Section 3.2. In computing $D_{KL}(p(y_{true}) || p(y))$, we specify $p(y_{true}) = N(X\beta_{true} + \mathbf{w}_{true}, \text{diag}(\sigma_{true}) \otimes I_k)$, which is the density of the true $y$ and $p(y) = N(X\beta + \mathbf{w}, \text{diag}(\sigma) \otimes I_k)$ is the density for $y$ from MDAGAR. While the ordering of the diseases does not appear to have a significant impact on model fitting as the density plots for the four orderings almost overlap with each other, (3) suggests that some order dependence may be expected.
FIGURE 7 Morán’s I of rth order neighbors for lung, esophageal, larynx, and colorectal cancer

FIGURE 8 Important county-level covariates with significant effects: Adult cigarette smoking rates (left), percentage of black residents (middle), and uninsured residents (right)

3.5 Model selection for different disease orders

We now evaluate the effectiveness of the method in Section 2.5 at selecting the model with the correct ordering of diseases. We used the bridgeampling package in R to compute \( p(M_t | y) = \max_{t=1, \ldots, 6} p(M_t | y) \) for each of \( n = 50 \times 6 \) datasets generated as described in Section 3.1. Table 1 presents the probability of each model being selected for different true model scenarios. The probability of selecting the true model is shown in bold along the diagonal. Our experiment reveals that bridge sampling is extremely effective at choosing the correct order. It was able to identify the correct order between 78% and 90%, which is substantially larger than any of the probability of choosing any of the misspecified models.

4 MULTIPLE CANCER ANALYSIS FROM SEER

We now turn to analyzing an areal dataset using the MDAGAR model for four different cancers: lung, esophagus, larynx, and colorectal. The incidence of adenocarcinoma of lung and esophageal cancer have been found to share common risk factors and metabolic mechanisms.
The dataset consists of the four cancers: lung, esophagus, larynx, and colorectal, where the outcome developing second primary lung cancer. The dataset is extracted from the SEER patients with colon cancer. Meanwhile, patients with laryngeal cancer have also been reported to possess high risks of developing second primary lung cancer.

The posterior model probabilities for 24 models are shown in Table 2. Table 3 shows the posterior means (95% credible intervals) for parameters estimated from $M_{10}$ and BMA estimates for regression coefficients only for the SEER four cancer dataset.

### Table 2: The posterior model probabilities for 24 models

| Model | $p(M_1 | y)$ | $p(M_2 | y)$ | $p(M_3 | y)$ | $p(M_4 | y)$ | $p(M_5 | y)$ | $p(M_6 | y)$ | $p(M_7 | y)$ | $p(M_8 | y)$ |
|-------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
|       | 0.000       | 0.000       | 0.000       | 0.000       | 0.000       | 0.000       | 0.000       | 0.000       |

### Table 3: Posterior means (95% credible intervals) for parameters estimated from $M_{10}$ and BMA estimates for regression coefficients only for the SEER four cancer dataset

| Parameters | Model | Esophageal | Larynx | Colorectal | Lung |
|------------|-------|------------|--------|------------|------|
| Intercept  | $M_{10}$ | 16.76 (4.06, 29.56) | 6.37 (−1.16, 13.89) | 19.16 (−11.94, 49.72) | 28.68 (−18.3, 74.93) |
| Male (%)   | $M_{10}$ | −0.04 (−0.17, 0.09) | 0.00 (−0.07, 0.08) | 0.24 (−0.12, 0.60) | 0.14 (−0.57, 0.79) |
| White (%)  | $M_{10}$ | 0.14 (−0.06, 0.34) | 0.14 (0.03, 0.26) | −0.16 (−0.73, 0.39) | 0.15 (−1.06, 1.29) |

Note: Bold values signify that the 95% credible intervals exclude 0.

patients with colon cancer. Meanwhile, patients with laryngeal cancer have also been reported to possess high risks of developing second primary lung cancer. The dataset is extracted from the SEER Stat database using the SEER Stat statistical software. The dataset consists of the four cancers: lung, esophagus, larynx, and colorectal, where the outcome is the 5-year average age-adjusted incidence rates (age-adjusted to the 2000 U.S. Standard Population) per 100,000 population in the years from 2012 to 2016 across 58 counties in California, USA, as mapped in Figure 6. The maps exhibit preliminary evidence of correlation across space and among cancers. Cutoffs for the different levels of incidence rates are quantiles for each cancer. For all four cancers, incidence rates are relatively higher in counties concentrated in the middle northern areas including Shasta, Tehama, Glenn, Butte, and Yuba than those other areas. In general, northern areas have higher incidence rates than in the south. This is especially pronounced for lung cancer and esophagus cancer.
FIGURE 9  Maps of posterior results using BMA for lung, esophagus, larynx, and colorectal cancer in California including (A) posterior mean spatial random effects and (B) posterior mean incidence rates

FIGURE 10  Maps of posterior results using the highest probability model $M_{10}$ for lung, esophagus, larynx, and colorectal cancer in California including (A) posterior mean spatial random effects and (B) posterior mean incidence rates

For larynx cancer, while the highest incidence rates are in the northwest (Del Norte and Siskiyou counties), the incidence rates in the south are also at somewhat higher levels. For colorectal cancer, the edge areas at the bottom also exhibit high incidence rates.

As an exploratory tool to assess associations among the cancers, we calculate Pearson’s correlation for each pair of cancers by regarding incidence rates in different counties as independent samples and find Pearson’s correlation coefficient between the incidence of lung cancer and those of esophageal, larynx, and colorectal cancers to be 0.55, 0.46, and 0.46, respectively. Meanwhile, the correlation between esophageal and larynx cancer is 0.27. Next, to explore the spatial association for each disease, we calculate Moran’s I based upon $r$th order neighbors for each cancer and plot the areal correlogram. Defining distance intervals, $(0, d_1], (d_1, d_2], (d_2, d_3], \ldots$, the $r$th order neighbors refer to units with distance in $(d_{r-1}, d_r]$, that is, within distance $d_r$ but separated by more than $d_{r-1}$. The distance is the Euclidean distance from an Albers map projection of California. As shown in Figure 7, lung, esophageal, and colorectal cancers all present spatial patterns that initially diminish with increasing $r$ and eventually flatten close to 0. Overall, counties with similar levels of incidence rates tend to depict some spatial clustering.
FIGURE 11 Maps of posterior results (Case 1) using MCAR for lung, esophagus, larynx, and colorectal cancer in California including (A) posterior mean spatial random effects and (B) posterior mean incidence rates

We turn to model based inference using (7). We return to the MDAGAR, GMCAR, and MCAR, where neighbors are defined using shared borders. We analyze this dataset and separate the spatial correlation for each cancer from association among cancers with the following prior specifications,

\[
p(\eta, \rho, \tau, \sigma, w) = \prod_{i=1}^{q} Unif(\rho_i | 0, 1) \times \prod_{i=2}^{q} \prod_{j=1}^{i-1} N(\eta_{ij} | 0, 0.01I_2) \times \prod_{i=1}^{q} N(\beta_i | 0, 0.001I) \times \prod_{i=1}^{q} IG(1/\tau_i | 2, 0.1) \times \prod_{i=1}^{q} IG(\sigma_i^2 | 2, 1) \times N(w | 0, Q_w).
\]  

We also discuss a case excluding the risk factor (see Web Appendix B Section S.2.2.3).

For covariates, we include county attributes that possibly affect the incidence rates, including percentages of residents younger than 18 years old (young\(_{ij}\)), older than 65 years old (old\(_{ij}\)), with education level below high school (edu\(_{ij}\)), percentages of unemployed residents (unemp\(_{ij}\)), black residents (black\(_{ij}\)), male residents (male\(_{ij}\)), uninsured residents (uninsure\(_{ij}\)) and percentages of families below the poverty threshold (poverty\(_{ij}\)). All covariates are common for different cancers and extracted from the SEER\(^*\)Stat database\(^{48}\) for the same period, 2012 to 2016.

Since cigarette smoking is a common risk factor for cancers, adult smoking rates (smoke\(_{ij}\)) for 2014 to 2016 were obtained from the California Tobacco Facts and Figures 2018 database.\(^{50}\) Spatial patterns in the map of adult cigarette smoking rates, shown in Figure 8, are similar to the incidence of cancers, especially lung and esophageal cancers, the highest smoking rates are concentrated in the north. While some central California counties (eg, Stanislaus, Tuolumne, Merced, Mariposa, Fresno, and Tulare) also exhibit high rates, although there is clearly less spatial clustering of the high rates than in the north.

Since the order of cancers in the DAG specify the model, we fit all 4! = 24 models using (7) and compute the marginal likelihoods using bridge sampling (Section 2.5). By setting the prior model probabilities as \(p(M = M_t) = \frac{1}{24}\) for \(t = 1, 2, \ldots, 24\), we compute the posterior model probabilities using (9). These are presented in Table 2. We obtain BMA estimates using (14) with the weights in Table 2. Among all models, model \(M_{10}\) is selected as the best model with the largest posterior probability 0.577 and the corresponding conditional structure is [esophageal] × [larynx | esophageal] × [colorectal | esophageal, larynx] × [lung | esophageal, larynx, colorectal].

Table 3 is a summary of the parameter estimates including regression coefficients, spatial autocorrelation (\(\rho_i\)), spatial precision (\(\tau_i\)), and noise variance (\(\sigma_i^2\)) for each cancer. From \(M_{10}\) and BMA, we find the regression slopes for the percentage of smokers and uninsured residents are significantly positive and negative, respectively, for esophageal cancer. The negative association between percentage of uninsured and esophageal cancer may seem surprising, but is likely a consequence of counties exhibiting low incidence rates for esophageal cancer having a relatively large number of uninsured residents.
FIGURE 12 Maps of posterior mean spatial random effects (with no covariates) using the same order as $M_{10}$

(see top right in Figure 6 and the right most figure in Figure 8). Since esophageal cancer has low incidence rates, this association could well be spurious due to spatial confounding. Percentage of smokers is, unsurprisingly, found to be a significant risk factor for lung cancer, while the percentage of blacks seems to be significantly associated with elevated incidence of larynx cancer. In addition, we tend to see that percentage of population below the poverty level has a pronounced association with higher rates of lung and esophageal cancer.

Recall from Section 2.4 that $\rho_1$ is the residual spatial autocorrelation for esophageal cancer after accounting for the explanatory variables, while $\rho_i$ for $i = 2, 3, 4$ are residual spatial autocorrelations after accounting for the explanatory variables and the preceding cancers in the model $M_{10}$. From Table 3, we see that esophageal cancer exhibits relatively weaker spatial autocorrelation, while the residual spatial autocorrelations for larynx and colorectal cancers after accounting for preceding cancers are both at moderate levels of around 0.5. Similarly for the spatial precision $\tau_i$, larynx appears to have the smallest conditional variability while that for colorectal and lung are slightly larger.

For the posterior mean incidence rates and spatial random effects $w_i$, we present estimates from model $M_{10}$ and BMA. Figure 9A,B is maps of posterior mean spatial random effects and model fitted incidence rates for four cancers obtained from BMA, while Figure 10A,B shows maps of those from model $M_{10}$. The posterior mean incidence rates from BMA and $M_{10}$ are in accord with each other, and both present DAGAR-smoothed versions of the original patterns in Figure 6. For posterior means of spatial random effects, in general, the estimates from $M_{10}$ are similar to model averaged estimates, especially for lung and colorectal cancers, exhibiting relatively large positive values in the northern counties, where the incidence rates are high. However, for esophageal and larynx cancers we see slight discrepancies between $M_{10}$ and BMA in the north. The BMA estimates produce larger positive random effects, ranging between 0.1 and 0.5, in most counties, while $M_{10}$ produces estimates between 0 and 0.1 for esophageal cancer. More counties with random effects larger than 0.1 are estimated from $M_{10}$ for larynx cancer. We believe this is attributable, at least in part, to another competitive model, $M_{15} = [\text{larynx}] \times [\text{esophagus}] | [\text{larynx}] \times [\text{lung}] | [\text{larynx}, \text{esophagus}] \times [\text{colorectal}] | [\text{larynx}, \text{esophagus}, \text{lung}]$ (posterior probability 0.342), which contributes to the BMA. On the other hand, the effects of some important county-level covariates play an essential role in the discrepancy between the estimates of random effects and model fitted incidence rates for each cancer.
Recall from Section 2 that $\eta_{0ii}'$ and $\eta_{1ii}'$ reflect the associations among cancers that can be attributed to spatial structure. Specifically, larger values of $\eta_{0ii}'$ will indicate inherent associations unrelated to spatial structure, while the magnitude of $\eta_{1ii}'$ reflects associations due to spatial structure. Figure S.2 presents posterior distributions of $\eta_i$ for all pairs of cancers. We see from the distribution of $\eta_{043}$ that there is a pronounced nonspatial component in the association between lung and colorectal cancers. Similar, albeit somewhat less pronounced, nonspatial associations are seen between larynx and esophageal cancers and between lung and larynx cancers. Analogously, the posterior distributions for $\eta_{143}$ and $\eta_{132}$ tend to have substantial positive support suggesting substantial spatial cross-correlations between lung and colorectal cancers and between colorectal and larynx cancers. Interestingly, we find negative support in the posterior distributions for $\eta_{121}$ and $\eta_{142}$. The negative mass implies that the covariance among cancers within a region is suppressed by strong dependence with neighboring regions. This seems to be the case for associations between lung and esophageal cancers and between lung and larynx cancers.

Web Appendix B also presents supplementary analysis that excludes adult smoking rates from the covariates, which we refer to as “Case 2.” Figure S.3 shows estimated correlations between pairwise cancers in each of the 58 counties. The top row presents the correlations including smoking rates (“Case 1”) as has been analyzed here. The bottom row presents the corresponding maps for “Case 2.” Interestingly, accounting for smoking rates substantially diminishes the associations among esophageal, colorectal and lung cancers. These are significantly associated in “Case 2” but only lung and colorectal retain their significance after accounting for smoking rates.

We also implemented the order-free MCAR model (as described in Section 3.3) and presented the estimates of posterior mean incidence rates and spatial random effects in Figure 11. Compared with MDAGAR, the MCAR exhibits better fitting for colorectal cancer since the posterior incidence rates in Figure 11B is closer to those in the raw map (Figure 6), while MDAGAR seems to outperform MCAR for larynx cancer. Overall, the model fitting is comparable between MDAGAR and MCAR.

5 | DISCUSSION

We have developed a multivariate “MDAGAR” model in conjunction with a bridge sampling method to estimate spatial correlations for multiple correlated diseases. The MDAGAR is constructed hierarchically over areal units based on univariate DAGAR models. We demonstrate that MDAGAR tends to outperform GMCAR when association between spatial random effects for different diseases is weak or moderate. MDAGAR retains the interpretability of spatial autocorrelations, as in univariate DAGAR, separating the spatial correlation for each disease from any inherent or endemic association among diseases. While MDAGAR, like all DAG based models, is specified according to a fixed order of the diseases, we show that bridge sampling can effectively choose among the different orders and also provide BMA inference in a computationally efficient manner.

Our data analysis elicits how correlations between incidence rates for different cancers are impacted by risk factors. For example, eliminating adult cigarette smoking rates produces similar spatial patterns for the incidence rates of esophageal, lung and colorectal cancer. In addition, the significant correlation between lung and esophageal cancer, even after accounting for smoking rates, implies other inherent or endemic association such as latent risk factors and metabolic mechanisms. We also see that the MDAGAR based posterior estimates of the latent spatial effects in Figures 9A and 10A resemble those from MDAGAR without covariates (Figure 12), while the maps for the estimated incidence rates in Figures 9B and 10B account for the spatial variability of the covariates.

Future research will look at different constructions of graphical models for areal data. Examples can include defining $r$th order neighbors using distance metrics, as in Figure 7, and deriving alternate precision matrices. We also intend to address scalability with very large number of diseases. Here, common spatial factor models for areal data can be adapted to model the factors as DAGAR, thereby yielding classes of DAGAR based factor models. A very different approach will be to build scalable graphical models using two different graphs: one for areal units (CAR or DAGAR) and another undirected graph representing conditional independence among cancers. Multidimensional MRFs as well as developments analogous to recently introduced graphical Gaussian processes can be pursued for high-dimensional disease mapping. Finally, spatial confounding in multivariate disease mapping will be explored in the context of MDAGAR.

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CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT
All computer programs implementing the examples in this paper can be found in the public domain and downloaded from https://github.com/LeiwenG/Multivariate_DAGAR.

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