Geographically Weighted Cox Regression for Prostate Cancer Survival Data in Louisiana

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Abstract

The Cox proportional hazard model is one of the most popular tools in analyzing time-to-event data in public health studies. When outcomes observed in clinical data from different regions yield a varying pattern correlated with location, it is often of great interest to investigate spatially varying effects of covariates. In this paper, we propose a geographically weighted Cox regression model for sparse spatial survival data. In addition, a stochastic neighborhood weighting scheme is introduced at the county level. Theoretical properties of the proposed geographically weighted estimators are examined in detail. A model selection scheme based on the Takeuchi’s model robust information criteria (TIC) is discussed. Extensive simulation studies are carried out to examine the empirical performance of the proposed methods. We further apply the proposed methodology to analyze real data on prostate cancer from the Surveillance, Epidemiology, and End Results cancer registry for the state of Louisiana.

Keywords: Cox Model; Graph Distance; Sparse Spatial Survival Data; Stochastic Neighborhood Weighting

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1 Introduction

In public health and epidemiology studies, clinical data is often collected at small geographical levels such as towns and counties, and aggregated on a larger level such as states. Analysis of such datasets, while providing information on an overall level about covariate effects, assumes that covariates affect the outcome equally across different locations, regardless of the variation in local environment and local treatment. Ignoring these effects makes the estimation on the aggregated data sub-optimal when we are more interested in precisely modeling the covariate effects on a finer level. Allowing for spatially related covariate effects will lead to a more flexible analysis, and a clearer picture of the relationship between the response variable and the covariates. Several methods have been proposed for analyzing geographical patterns of survival data. One popular method is to treat the spatial variation as random effects in the model. For example, Banerjee et al. (2003) considered random effects corresponding to clusters that are spatially arranged in a frailty model. Banerjee and Dey (2005) developed a Bayesian hierarchical model that captures spatial heterogeneity in the framework of proportional odds. Zhang and Lawson (2011) added a random effect to the Bayesian accelerated failure time model with a conditional autoregressive prior to analyze prostate cancer data from Louisiana collected between 2000 and 2004, while Li et al. (2015) developed a Bayesian semiparametric approach to the extended hazard model to consider spatial effects on prostate cancer survival. The aforementioned works only considered spatial random effects on Bayesian survival models. Another popular approach involves allowing the coefficients of models to be spatially varying, and using a certain weighting scheme in estimating the coefficients for different locations. Gelfand et al. (2003) considered spatially varying coefficients in the context of Gaussian responses, and proposed a Gaussian process model to estimate the coefficients. Brunsdon et al. (1998) proposed an alternative approach where a weighting function, based on a certain measure of distance, is imposed on the observations, and the parameter estimates can be obtained from a weighted least squares
estimation. Nakaya et al. (2005) extended the idea to Poisson regression, and the parameter estimates are obtained by maximizing a weighted likelihood function.

For survival data with time-to-event structure, Hu and Huffer (2019) studied a spatially varying Nelson–Aalen estimator and Kaplan–Meier estimator with a geographically weighted estimating approach. Hu (2017) studied an accelerated failure time regression model with spatially varying coefficients in a Bayesian context. For the Cox proportional hazards model (Cox, 1972, 1975), Fan et al. (2006) studied time varying coefficients using a local partial-likelihood estimator. Geographically weighted survival models, however, are not fully studied in spatial survival analysis, and there is no existing literature studying the Cox model with spatially varying coefficients for geographically distributed survival data.

For geographically sparse data, simple data stratification by location (e.g., by county) is not feasible as the sample sizes may be too small to fit Cox models for some locations. In order to address this issue, we develop a geographically weighted Cox regression model following the first law of geography (Tobler, 1970). Similar to the idea from Brunsdon et al. (1996, 1998), we estimate the regression coefficients on each individual location (i.e., county) by maximizing the local partial-likelihood with subjects weighted according to their distance from this location. Greater weights are assigned to the nearby subjects, since intuitively, nearby regions will share similar environmental and social factors, which will have similar effects on the observations.

As with most geographically weighted methods, as recently reviewed in Murakami et al. (2019), the choice of weighting function, its associated bandwidth, and distance metric are all important. In the geographically weighted regression (GWR) context, Brunsdon et al. (1996) discussed different weighting functions, and the bandwidth is selected by minimizing the cross-validated out-of-sample sum of squared errors on a grid of candidate values. The choice of distance metric in GWR has been discussed by Lu et al. (2019); Oshan et al. (2019). White and Ghosh (2009) used a Stochastic Neighborhood Autoregressive (SNCAR) model
where observations that are beyond a certain threshold of distance are weighted downward. The choice of such threshold can be subtle, and can impact the final model estimation results. To overcome such complication, we consider the usage of graph distance (Müller et al., 1987; Bhattacharyya and Bickel, 2014) which yields a natural choice of threshold, provides robust estimation, and can be easily implemented. While cross-validation remains a popular approach for choosing bandwidths in the linear regression framework, prediction-based selection methods are not suitable in this scope as there is no response for the hazard, and only the parametric component of the hazard function is estimated by Cox regression using the partial likelihood approach. Therefore, a likelihood-based bandwidth selection approach is proposed. To account for the bias-variance tradeoff in addition to maximizing the partial likelihood, a modified Takeuchi information criterion (TIC; Takeuchi, 1976) is used in favor of the Akaike information criterion (AIC; Akaike, 1973).

The rest of this paper is organized as follows. In Section 2, data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry is introduced as a motivating example. In Section 3, we propose the geographically weighted Cox model, and modify the stochastic neighborhood weighting function of White and Ghosh (2009) for areal based data using the graph distance. Model selection based on TIC, as well as the theoretical properties of the estimators, are discussed in the same section. Simulation studies to illustrate the performance of our estimators are presented in Section 4. In Section 5, we apply our methods to survival analysis of patients diagnosed with prostate cancer from the SEER cancer registry for the state of Louisiana. We conclude the paper with a brief discussion in Section 6.

2 Motivating Example

The SEER Program provides information on cancer statistics in an effort to reduce the cancer burden among the U.S. population. We consider the prostate cancer data from July
to December 2005 diagnoses for Louisiana from their November 2014 submission (Hu and Huffer, 2019).

Due to Hurricane Katrina, the number of observations diagnosed between the second half of 2005 is noticeably smaller than for other years (1403 vs 1787 for July to December for years 2000-2012 except for 2005). The data being spatially sparse, these diagnoses are not analyzed in most SEER reportings. Except for the relatively small sample size, censoring rates and other descriptive measures of covariates presented in Table 1 are similar to the 2000 to 2004 dataset discussed in Zhang and Lawson (2011).

Together with the covariates, survival times, final statuses, and county locations of these observations are also reported. Only events due to prostate cancer are considered. Figure 1 presents the number of diagnoses, and the Kaplan–Meier estimate of survival probability at 50 months after diagnosis in the 64 counties of Louisiana. The distributions of the covariates from different counties are very similar. The Kaplan–Meier estimate of survival probability, however, shows a spatially varying pattern across counties, which is similar to observations made in Hu and Huffer (2019). In order to capture the spatial heterogeneity of the hazard rate, we consider the Cox model with spatially varying coefficients.

3 Methodology

3.1 Geographically Weighted Cox Model

We first consider the case where the precise location of each observation is available, and is represented in (latitude, longitude) pairs. Let \((T_i, \delta_i, Z_i, s_i), i = 1, ..., n\), denote an independent sample of right-censored survival data from different sites, where \(T_i\) is a right-censored event time and \(\delta_i = I(T_i^* \leq C_i)\) with \(T_i^*\) being the true survival time and \(C_i\) being the censoring time, \(Z_i \in \mathcal{R}^p\) is the corresponding vector of covariates, and \(s_i \in \mathcal{R}^2\) is the corresponding
Table 1: Demographic characteristics for Louisiana data. For continuous variables, the mean and standard deviation (SD) are reported. For binary variables, the frequency and percentage of each class are reported.

| Mean (SD)/ Frequency (Percentage) |
|-----------------------------------|
| Age 66.21 (11.25)                  |
| Survival Time 72.36 (25.54)       |
| Event 32.41 (24.17)               |
| Censor 76.01 (22.35)              |
| Marital Status                    |
| Currently Married 857 (67.11%)    |
| Other 420 (32.89%)                |
| Race                              |
| Black 379 (29.68%)                |
| Other 898 (70.32%)                |
| Cause-specific Death Indicator    |
| Event 107 (8.38%)                 |
| Censor 1170 (91.62%)              |

Figure 1: (a) Number of diagnoses in counties of Louisiana; (b) Kaplan–Meier estimate of survival probability at 50 months after diagnosis.
location, i.e., \( s_i = (\text{latitude}_i, \text{longitude}_i) \). In the proportional hazards model, estimation of \( \beta \) is achieved via maximization of the partial likelihood (using notation of Fleming and Harrington, 1991):

\[
\text{PL}(\beta) = \prod_{i=1}^{n} \prod_{t \geq 0} \left[ \frac{Y_i(t) \exp \left( Z_i^T \beta \right)}{\sum_j Y_j(t) \exp \left( Z_j^T \beta \right)} \right] ^{dN_i(t)},
\]

(1)

where \( Y_i(t) = I(T_i \geq t) \), \( N_i(t) \in \{0, 1\} \) is the count of events for subject \( i \) at time \( t \), and \( dN_i(t) = I(T_i \in [t, t + \Delta), \delta_i = 1) \), where \( \Delta \) is chosen to be very small such that \( \sum_{i=1}^{n} dN_i(t) \leq 1 \) for any \( t \).

This estimation scheme essentially assigns equal weights to all observations. As mentioned in the introduction, estimating regression coefficients for each county in the Cox model by using only observations within that county is often not feasible, as in many cases (e.g., for relatively rare diseases) there are not enough observations from one particular county to fit the model. We thus propose a geographically weighted Cox model, inspired from the work of Brunsdon et al. (1998), using a modified local partial likelihood at a general location \( s \) is given by

\[
\text{PL}(\beta(s)) = \prod_{i=1}^{n} \prod_{t \geq 0} \left[ \frac{w_i(s)Y_i(t) \exp \left\{ Z_i^T \beta(s) \right\}}{\sum_j w_j(s)Y_j(t) \exp \left\{ Z_j^T \beta(s) \right\}} \right] ^{dN_i(t)},
\]

(2)

where \( w_i(s) \) is the geographical weight calculated using the distance between \( s \) and \( s_i \). The choice of weight and distance measure will be discussed in Section 3.2 below. Setting the first order derivatives of \( \log \text{PL}(\beta(s)) \),

\[
\frac{\partial \log \text{PL}(\beta(s))}{\partial \beta(s)} = \sum_{i=1}^{n} \delta_i \left( w_i(s)Z_i - \frac{\sum_{j \in R(T_i)} w_j(s)Z_j \exp \left\{ Z_j^T \beta(s) \right\}}{\sum_{j \in R(T_i)} w_j(s) \exp \left\{ Z_j^T \beta(s) \right\}} \right),
\]

(3)

to zero yields estimates of \( \beta(s) \) using the Newton-Raphson technique, where \( R(T_i) \) is the set
of observations with $Y_j(T_i) = 1$. We can also obtain the observed Fisher information of (2):

$$I(\beta(s)) = \sum_{i=1}^{n} \left[ \frac{\sum_{j \in R(T_i)} w_j(s) [\exp\{Z_j^\top \beta(s)\}]^2 Z_j Z_j^\top}{\left( \sum_{j \in R(T_i)} w_j(s) \exp\{Z_j^\top \beta(s)\} \right)^2} - \frac{\sum_{j \in R(T_i)} w_j(s) \exp\{Z_j^\top \beta(s)\} Z_j Z_j^\top}{\sum_{j \in R(T_i)} w_j(s) \exp\{Z_j^\top \beta(s)\}} \right].$$

(4)

### 3.2 Stochastic Neighborhood Weighting Function

We now review some traditional weighting schemes for geographically weighted regression. Suppose again, for now, that the precise (latitude, longitude) location of each observation is available. As in Hu (2017) and Hu and Huffer (2019), a natural way to account for the locality is setting the weights to zero if the location of the observation exceeds some threshold $d$ from the location whose vector of coefficients we want to estimate. This induces the weighting scheme:

$$w_i(s) = \begin{cases} 
1 & d_i(s) < d \\
0 & \text{otherwise}
\end{cases},$$

(5)

where $d_i(s)$ is a certain measure of distance between locations $s_i$ and $s$. These weights are the simplest to calculate, but are discontinuous as a function of the distance between the two locations. Alternatively, we may use the exponential function or Gaussian function to compute continuous weights:

$$w_i(s) = \exp(-d_i(s)/h) \quad \text{exponential}$$

$$w_i(s) = \exp(-d_i(s)/h)^2 \quad \text{Gaussian}$$

where $h > 0$ is a bandwidth parameter chosen by the user. Both weighting functions are decreasing with respect to the distance between two locations. The bi-square kernel, which
takes the form

\[ w_i(s) = \begin{cases} 
1 - (d_i(s)/d)^2 & |d_i(s)| < d \\
0 & \text{otherwise}
\end{cases} \]

again with \( d \) being some threshold, has also been used in many works, including Brunsdon et al. (1996) and Oshan et al. (2019).

The weighting functions mentioned above are mainly appropriate for point-reference data where locations vary continuously over a spatial domain. The data considered in our study is areal data, where the spatial domain is a fixed subset (of regular or irregular shape), but now partitioned into a finite number of areal units (e.g., counties) with well-defined boundaries. One natural way to proceed is to locate all observations for a county to its “center”, for example, its centroid, and calculate a certain measure of distance between the county centroids, e.g., the great circle distance (Hijmans, 2017), or the Euclidean distances calculated based on the projected coordinates of county centroids (Oshan et al., 2019). Then based on such distance matrices, White and Ghosh (2009) proposed the SNCAR model, which is an extension of the ordinary Conditional Autoregressive (CAR; Banerjee et al., 2014) model. Unlike the general adjacency matrix, whose diagonal elements are all 0 and off diagonal element \( a_{ij} = 1 \) if areas \( A_i \) and \( A_j \) share a common boundary, the SNCAR model allows the off-diagonal elements to depend on unknown parameters, i.e.,

\[ a_{ij} = \begin{cases} 
1 & \text{if } 0 < d_{ij} \leq d_l \\
c(d_{ij}, h) & \text{if } d_l < d_{ij}
\end{cases} \] (6)

where \( c(d_{ij}, h) \) is some function such that \( c(d_{ij}, h) < 1 \) (e.g., \( c(d_{ij}, h) = \exp(-d_{ij}/h) \)), \( d_l \) is an unknown threshold for adjacency to be estimated, and \( d_{ij} \) is a certain measure of distance between \( A_i \) and \( A_j \). Such adjacency matrices can subsequently be used to assign weights to observations in different counties when we fit regression models for each particular county. It can be seen that the choice of distance function, as well as the distance measure, are both
critical in deciding the weights. Deciding on a threshold $d_l$ in (6) for the great circle distance or Euclidean distance, for example, involves determining how close is “close enough” to be considered the same, which is usually a subjective matter. In practice, it is often done with cross-validation such as in Brunsdon et al. (1998), which is highly data dependent. A more robust and natural distance function, as well as an associated rule, is desired. Therefore, as a solution to this problem, we propose the usage of the graph distance (Bhattacharyya and Bickel, 2014) in formulating adjacency matrices.

Following Müller et al. (1987) and Bhattacharyya and Bickel (2014), we denote a graph as $G$, with set of vertices $V(G) = \{v_1, \ldots, v_n\}$, and set of edges $E(G) = \{e_1, \ldots, e_m\}$. The graph distance between two vertices $v_i$ and $v_j$ is defined as follows:

$$d_{v_i v_j} = \begin{cases} |V(e)| & \text{if } e \text{ is the shortest path connecting } v_i \text{ and } v_j \\ \infty & v_i \text{ and } v_j \text{ are not connected} \end{cases}$$

(7)

where $|V(e)|$ represents the cardinality of edges in $e$. In this way, we can calculate the graph distance among the counties in the data set. In other words, we treat the spatial structure of Louisiana as a graph, and each county is represented as one vertex of this graph. The distance matrix of the 64 Louisiana counties in our study is provided in Figure 2 for illustration. Plugging in the graph distances into (6) yields a weighting function to assign a weight to observations in county $i$ when we fit a regression model for county $s$:

$$w_i(s) = \begin{cases} 1 & \text{if } d_{v_i v_s} \leq 1 \\ \exp(-d_{v_i v_s}/h) & \text{if } 1 < d_{v_i v_s} \end{cases}$$

(8)

where $d_{v_i v_s}$ is the graph distance between counties $i$ and $s$. This means that all observations in county $i$ will get the same weight value. The spatial weighting function in (8) will use all the information from adjacent counties, and the weight is a decreasing function of the
Figure 2: Visualization of graph distances for Louisiana counties. Darker colors indicate greater graph distances. The maximum graph distance is 11.

3.3 Model Assessment Criterion

The bandwidth $h$ in (8) should not be chosen arbitrarily. For Cox regression on a dataset where covariates are fixed but their effects are time-varying, Verweij and van Houwelingen (1995) suggested using partial likelihood based AIC for model selection. Here, as we are only concerned with bandwidth selection, the component of AIC accounting for model complexity remains the same across all models being compared, so that the log-partial likelihood would be the sole determinant of AIC values. The smallest bandwidth would always be preferred, as the model is driven to fit local data as closely as possible. The bias-variance trade-
off in introducing bias, while at the same time lowering volatility of per-county parameter estimates, is not taken into account. Therefore, we consider using the TIC. Using the generalized dimension of a model instead of simply the dimension of parameters, the TIC for a general model $M_l$ is defined as:

$$
\text{TIC}(M_l) = \max_{\theta_l} \left[ -2 \log(\mathcal{L}(M_l, \theta_l)) - 2 \text{Tr}(\mathcal{I}^{-1}(\theta_l) K(\theta_l)) \right],
$$

where $\mathcal{L}$ denotes the model likelihood, $\theta_l$ is the parameter in model $M_l$, $\mathcal{I}(\theta_l)$ is the information matrix for $\theta_l$, and $K(\theta_l) = U(\theta_l)U^\top(\theta_l)$ with $U(\theta_l)$ being the score vector at $\theta_l$.

We consider the partial likelihood based TIC for the geographically weighted Cox model. For observed data with $J$ unique locations $s_1^*, \cdots, s_J^*$ and estimated regression coefficients $\hat{\beta}(s_1^*), \cdots, \hat{\beta}(s_J^*)$, for a particular bandwidth $h$, the TIC can be defined as:

$$
\text{TIC}(h) = -2 \sum_{j=1}^J \sum_{1 \leq i \leq n,s_i = s_j^*} \delta_i \left\{ Z_i^\top \hat{\beta}(s_j^*) - \log \left[ \sum_{k \in \mathcal{R}(T_i)} \exp\left( Z_k^\top \hat{\beta}(s_j^*) \right) \right] \right\} + 2 \sum_{j=1}^J \text{Tr} \left( \mathcal{I}^{-1}(\hat{\beta}(s_j^*)) K_j(\hat{\beta}(s_j^*)) \right),
$$

where $\mathcal{I}^{-1}(\hat{\beta}(s_j^*))$ is the observed information matrix in (4) evaluated at $\hat{\beta}(s_j^*)$, and $K_j(\hat{\beta}(s_j^*)) = U_j(\hat{\beta}(s_j^*))U_j(\hat{\beta}(s_j^*))^\top$ is the variance matrix for the score vector based on observations at $s_j^*$, which can be calculated as:

$$
U_j(\hat{\beta}(s_j^*)) = \sum_{i=1}^{n_j} \int_0^{\infty} [Z_i - \overline{Z}(\hat{\beta}(s_j^*), t)]dN_i(t),
$$

where $n_j$ is the number of observations at $s_j^*$, and $\overline{Z}(\hat{\beta}(s_j^*), t)$ is the weighted vector of covariates of these observations still alive at time $t$, with the weights being their risk scores, $\exp\{Z_i^\top \hat{\beta}(s_j^*)\}$. We can select the bandwidth with the smallest TIC calculated by (10). In our Louisiana dataset, the $s_j^*$’s correspond to the centroids of the 64 counties.
3.4 Asymptotic Results

The following regularity conditions are required to establish consistency of the estimator and the asymptotic distribution of the estimator:

C1 Conditions A1 to A8 in Fan et al. (2006).

C2 $w_i(s), i = 1, \cdots, n$ follow regularity conditions of Theorem 3.2 in Wang and Yao (2006).

Condition C1 and C2 will be used to derive the pointwise convergence properties of $\hat{\beta}(s)$ and its asymptotic normality. Condition C2 will be used to derive the bias term of $\hat{\beta}(s)$ in Proposition 2 below and has regularity constraints on the geographical weights. The proofs are provided in the Supplemental Material.

**Proposition 1.** Under condition C1, we have:

$$\hat{\beta}(s) \xrightarrow{p} \beta(s),$$

for any $s \in \mathbb{R}^2$.

**Proposition 2.** Under conditions C1 and C2, we have:

$$\sqrt{n}(\hat{\beta}(s) - \beta(s) - \xi(s)) \xrightarrow{L} N(0, \Sigma(s)),$$

for any $s \in \mathbb{R}^2$, where $\xi(s)$ is bias of $\hat{\beta}(s)$ defined as $b_{nw}$ in Theorem 3.2 in Wang and Yao (2006), and $\Sigma(s)$ is the asymptotic variance covariance matrix.

4 Simulation Study

In this section, we use simulated survival datasets that resemble the SEER data to study the performance of the proposed method when the observations are generated with and
without spatially varying coefficients. All calculations are performed in R, using the `survival` package (Therneau, 2017). The code and related documentation is available at GitHub. Additional simulation studies have been conducted to verify the performance of the proposed methods for high censoring survival data, and the results are included in the Supplemental Material.

### 4.1 Simulation Without Spatially Varying Coefficients

We obtain the geographical information of Louisiana counties from the US Census Bureau. The same spatial correlation structure of counties from the real data is used in our simulation. In addition, to compare geographical distance based weighting schemes, the matrix of great circle distance (Hijmans, 2017) for the 64 county centroids is also calculated. As the maximum graph distance for Louisiana counties is 11, the great circle distances are also normalized to have a maximum value of 11 to make both distances comparable.

To begin, the number of observations for each county is randomly selected from 30 to 40 to give an expected sample size of 35 per county. The sample size is selected to be slightly larger than the average per county sample size in the real data, as we would like to obtain the local parameter estimates as well for comparison. Three covariates are considered: Age, (centered and scaled), Black, and Married, where Age ~ N(0.1), Black ~ Bernoulli(0.3), and Married ~ Bernoulli(0.7). Next, survival times are generated from a Cox model with baseline hazard $\lambda_0(t) = 0.03$, and vector of coefficients $\beta = (0.7, 0.5, -0.8)^\top$. Censoring times are generated independently using a mixture distribution $0.1\text{Uniform}(0, 60) + 0.9(60)$, where $0.1(60)$ represents a point mass at 60. The average censoring rate is around 40%. Weights based on the graph distance matrix (Figure 2) are calculated using the weighting scheme in (8). For the great circle distance, (6) is used with $c(d_{ij,j}) = \exp(-d_{ij}/h)$ and four candidate values for $d_l$: 0.5, 1, 2, and 1.29. The last threshold, $d_l = 1.29$ corresponds to the great circle distance based weight matrix which has same number of 1 entries as the graph.
distance based matrix from (8).

With the largest distance being 11, at \( h = 50 \), a county will have a relative weight of over 0.80 in estimating even the most distant county, and the performance of such a model is fairly close to a global model where all observations are used and weighed equally. Therefore, the grid of bandwidths considered is set to \( h \in \{0.5, 1, \ldots, 50\} \). For each county, we fit the geographically weighted Cox regression using the different aforementioned weighting schemes, a global (unweighted) Cox regression using all observations, and a local Cox regression using only observations within the particular county. The simulation process described above is repeated for \( r = 1000 \) times. The parameter estimates are evaluated using the following four measurements:

\[
\text{mean absolute bias (MAB)} = \frac{1}{64} \sum_{\ell=1}^{64} \frac{1}{1000} \sum_{r=1}^{1000} \left| \hat{\beta}_{\ell,m,r} - \beta_{\ell,m} \right|
\]

\[
\text{mean standard deviation (MSD)} = \frac{1}{64} \sum_{\ell=1}^{64} \left\{ \frac{1}{999} \sum_{r=1}^{1000} \left( \hat{\beta}_{\ell,m,r} - \bar{\beta}_{\ell,m} \right)^2 \right\}^{1/2}
\]

\[
\text{mean of mean squared error (MMSE)} = \frac{1}{64} \sum_{\ell=1}^{64} \frac{1}{1000} \sum_{r=1}^{1000} \left( \hat{\beta}_{\ell,m,r} - \beta_{\ell,m} \right)^2
\]

\[
\text{mean coverage probability (MCP)} = \frac{1}{64} \sum_{\ell=1}^{64} \frac{1}{1000} \sum_{r=1}^{1000} \left( 1 \left( \left| \hat{\beta}_{\ell,m,r} - \beta_{\ell,m} \right| \leq 1.96 \text{SE}(\hat{\beta}_{\ell,m,r}) \right) \right)
\]

where \( \hat{\beta}_{\ell,m,r} \) is the estimate for the \( m \)th coefficient of county \( \ell \) in the \( r \)th replicate, \( \bar{\beta}_{\ell,m} \) is the average of \( \hat{\beta}_{\ell,m,r} \) over the 1000 replicates, \( \beta_{\ell,m} \) is the true underlying parameter, and \( 1(\cdot) \) is the indicator function.

The four measurements are plotted against \( h \) in Figure 3. As seen from the graph, when there is no spatial variation in covariate effects, at large bandwidth values, the MAB, MSD and MMSE stabilize at very small values, while the MCP stays well above 0.95. The most frequently selected bandwidth by the graph distance based weighted models, i.e., the bandwidth that corresponds to the smallest TIC in the 1000 replicates, is 50, which is in
Figure 3: Performance measures for the geographically weighted Cox models fitted using different distance/threshold combinations when there is no spatial variation in covariate effects.

accordance with our expectation. With $d_l = 0.5$ and $d_l = 1$ in the great circle distance based models, the TIC is dominated by the likelihood component, and tends to select the smallest bandwidth possible ($h = 0.5$), where little neighboring information is take into account. The MAB, MSD and MMSE, however, are fairly large at this bandwidth. With $d_l = 1.29$ and $d_l = 2$, the great circle distance based models favor the largest bandwidth possible, and their performances are highly similar to the graph distance based model, as they all approximate a globally unweighted model.

### 4.2 Simulation with Spatially Varying Coefficients

To investigate the performance of the proposed methods in the presence of spatially varying coefficients, the same procedures as previously described are used to generate the covariates and censoring times.
Table 2: Performance of local, global, and best selected geographically weighted Cox regressions when there is no spatial variation in covariate effects. GD stands for graph distance, and GCD stands for great circle distance.

| Model                        | Parameter | MAB   | MSD   | MMSE  | MCP  |
|------------------------------|-----------|-------|-------|-------|------|
| Local                        | $\beta_1$ | 0.299 | 0.393 | 0.165 | 0.946|
|                              | $\beta_2$ | 0.586 | 1.163 | 1.409 | 0.944|
|                              | $\beta_3$ | 0.568 | 0.979 | 1.019 | 0.944|
| Global                       | $\beta_1$ | 0.027 | 0.034 | 0.001 | 0.949|
|                              | $\beta_2$ | 0.052 | 0.065 | 0.004 | 0.945|
|                              | $\beta_3$ | 0.053 | 0.065 | 0.004 | 0.953|
| GD Weighted, $h = 50$       | $\beta_1$ | 0.027 | 0.034 | 0.001 | 0.962|
|                              | $\beta_2$ | 0.052 | 0.066 | 0.004 | 0.951|
|                              | $\beta_3$ | 0.053 | 0.065 | 0.004 | 0.960|
| GCD Weighted, $d_l = 0.5, h = 0.5$ | $\beta_1$ | 0.114 | 0.143 | 0.021 | 0.993|
|                              | $\beta_2$ | 0.219 | 0.274 | 0.078 | 0.992|
|                              | $\beta_3$ | 0.218 | 0.272 | 0.077 | 0.988|
| GCD Weighted, $d_l = 1, h = 0.5$ | $\beta_1$ | 0.106 | 0.133 | 0.019 | 0.965|
|                              | $\beta_2$ | 0.201 | 0.252 | 0.066 | 0.967|
|                              | $\beta_3$ | 0.200 | 0.251 | 0.066 | 0.960|
| GCD Weighted, $d_l = 1.29, h = 50$ | $\beta_1$ | 0.027 | 0.034 | 0.001 | 0.962|
|                              | $\beta_2$ | 0.052 | 0.066 | 0.004 | 0.951|
|                              | $\beta_3$ | 0.053 | 0.065 | 0.004 | 0.960|
| GCD Weighted, $d_l = 2, h = 50$ | $\beta_1$ | 0.027 | 0.034 | 0.001 | 0.961|
|                              | $\beta_2$ | 0.052 | 0.066 | 0.004 | 0.950|
|                              | $\beta_3$ | 0.053 | 0.065 | 0.004 | 0.959|
Figure 4: Performance measures for the geographically weighted Cox models fitted using different distance/threshold combinations when the covariate effects are spatially varying as in (11).

We first consider a scenario where the vector of coefficients depend on the geospatial location of the 64 county centroids (latitude, longitude). Same as before, the same 7 models are fitted and 1000 replicates of simulation are performed. For data generation, to simulate smooth variation over adjacent locations, for county $\ell$, $\ell = 1, \ldots, 64$, we let the $\beta$ vector for county $\ell$ be the transpose of

$$
(0.7, 0.5, -0.8) + 0.15 \times (\text{latitude}_\ell - \overline{\text{latitude}} + \text{longitude}_\ell - \overline{\text{longitude}}).
$$

(11)

The range for each true coefficient is around 0.72, and censoring rates in the generated 64,000 blocks of data range from 16.7% to 90.9%. Again, a visualization of the performance measures is given in Figure 4. It can be seen that the performance of great circle distance based models is influenced by the threshold $d_l$. At small bandwidths, a small $d_l$ (0.5, for example) gives rise to a weighting scheme such that the model produces unstable parameter estimates for each county, while no weighting scheme based on a large $d_l$ (2, for example)
Table 3: Performance of local, global, and best selected geographically weighted Cox regressions when covariate effects vary spatially according to (11).

| Model                        | Parameter | MAB  | MSD  | MMSE | MCP  |
|------------------------------|-----------|------|------|------|------|
| Local                        | $\beta_1$ | 0.303| 0.400| 0.171| 0.946|
|                              | $\beta_2$ | 0.607| 1.255| 1.806| 0.946|
|                              | $\beta_3$ | 0.571| 1.007| 1.085| 0.945|
| Global                       | $\beta_1$ | 0.134| 0.036| 0.027| 0.298|
|                              | $\beta_2$ | 0.141| 0.067| 0.031| 0.528|
|                              | $\beta_3$ | 0.139| 0.065| 0.030| 0.537|
| GD Weighted, $h = 1$         | $\beta_1$ | 0.079| 0.088| 0.010| 0.956|
|                              | $\beta_2$ | 0.139| 0.170| 0.031| 0.971|
|                              | $\beta_3$ | 0.138| 0.168| 0.031| 0.971|
| GCD Weighted, $d_l = 0.5, h = 0.5$ | $\beta_1$ | 0.105| 0.129| 0.018| 0.992|
|                              | $\beta_2$ | 0.200| 0.250| 0.066| 0.993|
|                              | $\beta_3$ | 0.197| 0.246| 0.063| 0.993|
| GCD Weighted, $d_l = 1, h = 1$ | $\beta_1$ | 0.074| 0.076| 0.009| 0.964|
|                              | $\beta_2$ | 0.125| 0.146| 0.025| 0.982|
|                              | $\beta_3$ | 0.123| 0.144| 0.024| 0.982|
| GCD Weighted, $d_l = 1.29, h = 1$ | $\beta_1$ | 0.073| 0.076| 0.009| 0.948|
|                              | $\beta_2$ | 0.125| 0.146| 0.025| 0.970|
|                              | $\beta_3$ | 0.122| 0.144| 0.024| 0.972|
| GCD Weighted, $d_l = 2, h = 1$ | $\beta_1$ | 0.073| 0.068| 0.009| 0.880|
|                              | $\beta_2$ | 0.115| 0.130| 0.021| 0.938|
|                              | $\beta_3$ | 0.113| 0.128| 0.021| 0.941|
Figure 5: Performance measures for the geographically weighted Cox models fitted using different distance/threshold combinations when the covariate effects are spatially varying as in (12).

can produce parameter estimates that have reasonable coverage probability. As can be seen from the graphs, there is a certain “sweet zone” of bandwidths, where appropriate amount of information is taken from neighbors, such that the geographically weighted parameter estimates have small MAB, MSD and MMSE. This is where an appropriate balance between bias and variance is achieved. Similar to Table 2, we recorded the most frequently selected bandwidth by TIC, and report the corresponding performance measures, together with those for the local and global Cox regressions, in Table 3. At $d_l = 0.5$, the optimal bandwidth selected by TIC for the great circle distance based models is again 0.5, while at the other three $d_l$ values, 1 becomes the most frequently chosen bandwidth. Given the performance of the graph distance based model with $h = 1$, we see it has better estimation than the great circle distance based model with $d_l = 0.5$, comparable performance to those with $d_l = 1$ or $d_l = 1.29$, and better coverage than that with $d_l = 2$.

In another scenario, instead of having the true covariate effects depend on geographical
Table 4: Performance of local, global, and best selected geographically weighted Cox regressions when covariate effects vary spatially according to (12).

| Model                        | Parameter | MAB   | MSD   | MMSE  | MCP  |
|------------------------------|-----------|-------|-------|-------|------|
| Local                        | $\beta_1$ | 0.308 | 0.411 | 0.181 | 0.945|
|                              | $\beta_2$ | 0.692 | 1.562 | 3.336 | 0.947|
|                              | $\beta_3$ | 0.611 | 1.266 | 1.914 | 0.947|
| Global                       | $\beta_1$ | 0.277 | 0.036 | 0.103 | 0.114|
|                              | $\beta_2$ | 0.278 | 0.069 | 0.104 | 0.226|
|                              | $\beta_3$ | 0.276 | 0.066 | 0.103 | 0.230|
| GD Weighted, $h = 1$         | $\beta_1$ | 0.084 | 0.088 | 0.011 | 0.944|
|                              | $\beta_2$ | 0.144 | 0.171 | 0.034 | 0.969|
|                              | $\beta_3$ | 0.140 | 0.168 | 0.032 | 0.969|
| GCD Weighted, $d_l = 0.5, h = 0.5$ | $\beta_1$ | 0.110 | 0.131 | 0.019 | 0.990|
|                              | $\beta_2$ | 0.204 | 0.253 | 0.068 | 0.993|
|                              | $\beta_3$ | 0.200 | 0.247 | 0.065 | 0.993|
| GCD Weighted, $d_l = 1, h = 1$ | $\beta_1$ | 0.085 | 0.075 | 0.011 | 0.925|
|                              | $\beta_2$ | 0.132 | 0.147 | 0.028 | 0.974|
|                              | $\beta_3$ | 0.127 | 0.144 | 0.026 | 0.975|
| GCD Weighted, $d_l = 1.29, h = 1$ | $\beta_1$ | 0.083 | 0.076 | 0.011 | 0.903|
|                              | $\beta_2$ | 0.131 | 0.147 | 0.028 | 0.961|
|                              | $\beta_3$ | 0.127 | 0.145 | 0.026 | 0.962|
| GCD Weighted, $d_l = 2, h = 1$ | $\beta_1$ | 0.085 | 0.069 | 0.012 | 0.813|
|                              | $\beta_2$ | 0.124 | 0.131 | 0.025 | 0.919|
|                              | $\beta_3$ | 0.121 | 0.130 | 0.024 | 0.921|
locations, we generate the true parameter vectors based on graph distance. The county St. Charles is selected as baseline with true parameter vector $(0.7, 0.5, -0.8)\top$. It is chosen as it is located among a cluster of relatively small counties, so that geographically close counties can have a large between county graph distance. For another county $\ell$, the parameter vector is the transpose of

$$(0.7, 0.5, -0.8) + 0.12 \times (\text{the graph distance between county } \ell \text{ and St. Charles}) - \text{mean of graph distance between all other counties and St. Charles) \quad (12)$$

The produced coefficients for each covariate have a range of 1.08. Censoring rates in generated data blocks range from 12.9% to 94.3%. The corresponding results are presented in Figure 5 and Table 4. Again, similar to in Figure 4, the tradeoff between bias and variance is clear. The performance of the graph distance based models is fairly robust - MAB, MSD and MMSE of parameter estimates are greatly reduced, while the MCP is maintained at around 0.95. The great circle distance based models, however, perform rather differently when different $d_l$ values are used. At $d_l = 1.29$ and $d_l = 2$, their performance is fairly similar to the graph distance based model. Indeed, while a good balance between bias and variance can also be found with great circle distance based models with an appropriate threshold $d_l$ and bandwidth $h$, the graph distance based models bypass the need to select a threshold and only require selection of $h$.

5 Real Data Analysis

We consider the prostate cancer data for Louisiana from the SEER Program. As in Onicescu and Lawson (2018), we exclude observations that have unknown ending statuses or unknown survival times, resulting in 1,277 complete observations. Descriptive statistics for the dataset
Figure 6: TICs calculated for geographically weighted Cox models plotted against their respective bandwidths.

are presented in Table 1. We consider the same three covariates as in data simulation, i.e., Age, Black, and Married.

We use the proposed weighted technique to obtain parameter estimates for each of the 64 counties. In addition to utilizing the graph distance, we also use the matrix of great circle distance between the county centroids for comparison. The same normalization is done to make the two distances comparable. Based on the simulation results, setting \( d_l = 0.5 \) for great circle distance tends to produce unstable parameter estimates for each county. Therefore, only 1, 1.29 and 2 are considered for candidate \( d_l \) values. Bandwidths \( h \in \{0.5, \ldots, 20\} \) are considered, as we have seen in simulation studies that model performances are rather stable beyond \( h = 20 \). For each \( h \), we calculated the TIC as in (10). As much as we want to make performance comparisons of the obtained parameter estimates and local estimates, such comparison is impossible, as four of the 64 counties had less than three observations, and local estimates for these counties cannot be obtained. Nevertheless, we are able to calculate the score vectors using per-county data, and calculate the TIC for bandwidth selection. The TICs are plotted against their corresponding bandwidths in
Figure 7: Parameter estimates (panel (a)), and their corresponding Z statistics (panel (b)) obtained from the geographically weighted Cox model for Louisiana counties using $h = 1.5$.

Figure 6. The TIC for the graph distance-based model is minimized at around $h = 1.5$ with a value of 672.4, where we have a good balance of bias and variance. When $h$ further increases, the TIC also increases, as larger bandwidths incur larger within-county biases.

For great circle distance based model at $d_l = 1$, $h = 0.5$ is selected, with a minimized TIC value of 671.6. When the threshold $d_l$ is further increased to 1.29, the TIC values show a monotonically decreasing trend, and favors the largest bandwidth, 20, with corresponding TIC value 674.7. Finally, at $d_l = 2$, the minimum TIC is attained at $h = 1.5$, with value 673.3. In addition, as there are counties with no events or only few observations, the local regressions could not be performed, but the global Cox regression can be fitted. The resulting TIC has a value of 674.7. Again, the performance of the great circle distance based models depends on the choice of threshold, which further influences the result of bandwidth selection. The graph distance, however, induces a natural weighting scheme that remains robust and provides credible estimation results.
The parameter estimates of the final model based on graph distance and with $h = 1.5$ corresponding to each county are plotted in panel (a) of Figure 7, together with their corresponding Z statistics ($\hat{\beta}_{\ell,i}/SE(\hat{\beta}_{\ell,i})$ for $\ell = 1, \ldots, 64$ and $i = 1, 2, 3$) plotted in panel (b). It can be easily observed that the effects of all three covariates are geographically varying. All parameters for **Age** are positive, indicating that increase in age brings higher hazard in all counties, which is in accordance with our intuition. Compared with other races, black males have been observed to have higher hazard, which could be of interest for studies on racial disparities in healthcare outcomes. In 61 of all 64 counties, married males have lower hazard for dying of prostate cancer. In the other three counties, the increasing effect is minor ($\hat{\beta}_{\text{Marriage}} = 0.09, 0.12$ and $0.03$, and neither significantly different from 0).

6 Discussion

In this paper, we proposed a geographically weighted Cox regression model to allow for varying coefficients at the local or subregional level, and corresponding partial likelihood based selection criterion for choosing the required bandwidth. In the simulation study, under the null scenario where there is no geographical variation in the covariate effects, we find that our method performed better than the local stratification estimation, which only used the observations within each county, and has similar performance with models that use the great circle distance weighted scheme and global estimation scheme. When simulating under scenarios in which there was spatial variation in covariate effects, the proposed selection criterion effectively selected the model with parameter estimates that have small within county variance yet still maintain high average coverage probability. In comparison, great circle distance based models perform differently when the threshold is set different values. The graph distance based models, however, do not suffer from this issue. The findings from the survival analysis of SEER prostate cancer patients are clearly appealing. Despite the sparsity of data, we are able to obtain parameter estimates for all 64 counties. Compared
to the great circle distance, the graph distance, together with its natural threshold of 1 in defining being “close enough”, provides a robust weighting scheme that produces models which achieve an appropriate balance between the bias and variance of parameter estimates for each location.

For future work, we will concentrate more on the following aspects. First, our bandwidth selection method is based on the TIC using the partial likelihood. Other criteria that focus on prediction, such as cross-validation methods, are worth investigating. Second, we assume all the regression coefficients are spatially varying. In practice, some regression coefficients may not be spatially varying. Identifying which coefficients are spatially varying, and estimating the Cox model with both spatially varying coefficients and spatially constant coefficients, such as in Mei et al. (2004) for linear regression, are another two important areas for future exploration. The implementation of standard tests for the proportional hazards assumption, such as that in Grambsch and Therneau (1994), in the context of spatially varying coefficients, is also worth investigating. In addition, when there is a large number of covariates, it may be of interest to develop a geographically penalized Cox regression model for variable selection. Finally, in this work, each covariate is weighed using the same value of bandwidth. Multiscale GWR, which allows each covariate to be weighed differently and allows more model flexibility, has been proposed recently by Fotheringham et al. (2017), and implemented in Python by Oshan et al. (2019). Yu et al. (2019) re-framed the multiscale GWR as an additive model and enabled inference for parameters estimates. Multiscale geographically weighted survival models, such as Cox model and the accelerated failure time model, are also devoted to future research.

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