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Space Time Model for Cancer Incidences in Tamilnadu: Mapping Health Statistics for Policy Programming and Decision Making

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Abstract*— *The burden of cancer is growing globally and is one of the top leading causes of death. Information on cancer patterns is essential for effective planning of cancer control interventions. In specific the geographical study of cancer will help in identifying the high risk communities for further etiological studies. The objective of the present study is to analyze the time based geographical expansion of cancer incidences in the study region. The spatial-temporal model using Knox and Mantel statistic was applied to identify if additional cases are added in subsequent time period from high incidence areas or from moderate areas or from low incidence areas. This study will provide an indication to any association between time trend and cancer incidences. Through the spatial temporal model, the high risk areas have been identified and the temporal variations in the risky zones were assessed
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Keywords*— *Include at least 5 keywords or phrases

I. INTRODUCTION

This Epidemic risk is a dynamic phenomenon with changing geographic pattern based on the temporal variations in determinant factors including structure of the community and other eco-epidemiological characteristics of areas. Disease mapping has been increasingly used to identify spatial patterns with the aid of GIS. Comparable maps in space and time can give valuable information not only about the present geographically localized disease problems but also on the evolution of these problems. Spatial models are very useful to model the disease occurrence (i.e. incidence or mortality) with a spatially varying rate, which is a product of an expected occurrence count and a relative risk. Exploratory spatial tools, has been valuable for the studies of geographic and environmental epidemiology especially when the causes of the disease and their determinant process are not clear (Rushton, 1998; Lawson *et al.*, 1999; Elliott *et al.*, 2000).

Space time clustering is an interaction between the places of onset and the times of onset of the disease (Williams, 1984). The presence of longitudinal information and spatially referenced data for any epidemic encourages the study and development of new models and several efforts have been already done in this direction. The application of GIS in conjugation with space-time statistics provides visual and quantitative information in relation to disease data. Bernardinelli *et al.* (1995) proposed a model in which both area specific intercept and temporal trend are modeled as random effects. Bohning (2003) incorporated the time dimension to the Poisson discrete mixture model in Schlattmann and Bohning (1993). Hsu *et al.* (2004) evaluated the disparity of female breast cancer mortality among racial groups by spatiotemporal analysis.

Spatiotemporal approach will be more relevant in understanding the environmental etiology of cancers, since lifetime cumulative exposures at critical times may be more strongly associated with risk for cancer than exposure from the recent period. Sheehan *et al.*, (2004) analyzed geographical and temporal variations in the proportion of late stage breast cancer in Massachusetts, 1988 to 1997. Han *et al.* (2005) investigated breast cancer risk associated with life time residential history using GIS based exploratory spatial analysis. The risk surfaces were assessed for both pre-menopausal and post-menopausal breast cancer and observed stronger evidence of geographical clustering for pre-menopausal women than for post menopausal women. Hsu *et al.* (2007) used spatial scan statistic (developed by Kullodrff) to determine the prostate cancer mortality disparities by geographic region over time in population subgroups in Texas. Zurriaga *et al.* (2008) studied the spatio-temporal distribution of lung cancer mortality for women in order to gain some insight into the factors, such as migration, that have had an influence on non-homogenous distribution pattern.

The main objective of the present is to identify the spatial effects based on two components i.e., the overall difference among the regions and the rate of change over time. To analyze such data, fixed and random effect model was used for the western part of Tamil Nadu as a case study using a spatio-temporal model.

II. STUDY AREA DESCRIPTION

The data for the present cross-sectional study was collected from the records of NCRP, as well as recognized cancer hospitals from the western region of Tamil Nadu for six years from 2001 to 2006. The western region of Tamil Nadu includes the districts Old Coimbatore, Erode, Namakkal, Salem and Nilgiris (Figure 1). There are twenty-nine

taluks(sub-unit of a district) from the five districts in the western region of Tamil Nadu. The necessary attributes from the oncology case sheets were entered into a database.

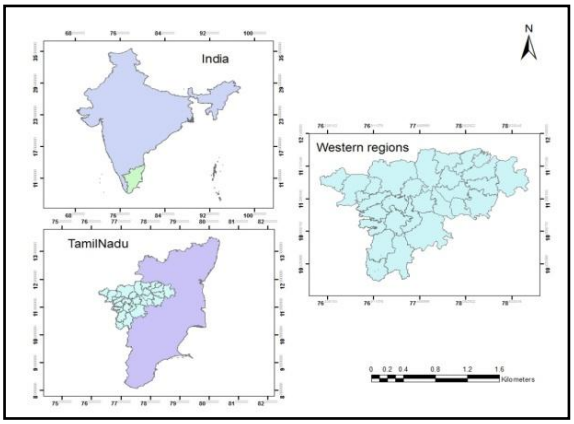


Figure 1: Study area location

The toposheets 58A, 58B, 58E, 58F and 58I from SOI (Survey of India), Government of India, covering the western region of Tamil Nadu were used in the preparation of base map with the scale of 1:250,000. The individual cancer cases were geo-coded using Google Maps, Google Earth and a GPS (Global Positioning System).

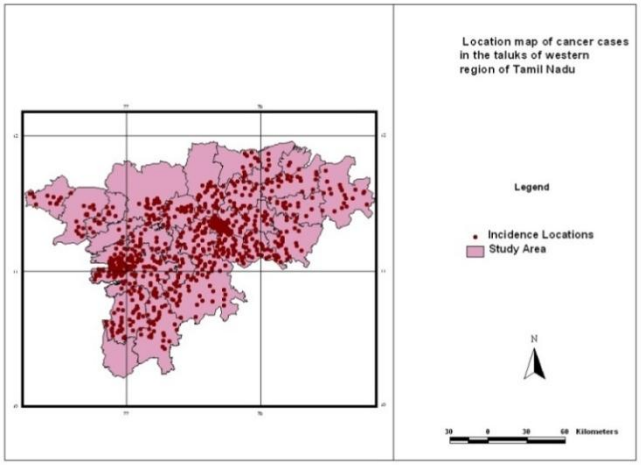


Figure 2: Geo-coded map of cancer incidences

III. METHODOLOGY AND RESULTS

To visualize the spatial effects based on two components i.e. the overall difference among the regions and the rate of change over time for these regions, a spatio-temporal analysis for fixed and random effects is performed. The conditional autoregressive model is used to model the random effects. Markov Chain Monte Carlo (MCMC) simulation is used for calculating the posterior and predictive quantities of interest. This allows a more general time trend by considering an auto regressive prior to temporal effects. CrimeStat software (CrimeStat III, 2004) was used to analyze statistically and ArcGIS 9.1 was used to map the results.

1. Knox Index

Knox and Bartlett (1964) developed the first technique to identify spatio-temporal clustering of disease events. Knox's test has formed the platform from which subsequent tests have been developed and it is a simple comparison of the relationship between incidences in terms of distance (space) and time. In this method, pairs of cases separated by less than a user-defined critical space-distance are considered to be near in space, and pairs of cases separated by less than a user-defined critical time-distance are said to be near in time. This classification allows pairs of points to be assigned to one of four cells in a 2 x 2 contingency table (near space-near time, near space-far time, far space-near time, far space-far time) and a test statistic is calculated as the number of pairs of cases that are near to one another in both space and time. Knox and Bartlett (1964) apply this method to data on cases of childhood Leukemia in Northeast England, finding significant evidence of space-time clustering. Valaramathi *et al* (2008)) has applied Knox Index to identify breast cancer risk in Tamil Nadu.

Table 1: Logical Knox Index (Observed)

	Close in time	Not close in time	
Close in distance	O_1	O_2	S_1
Not close in distance	O_3	O_4	S_2
	S_3	S_4	N

where N= O_{1+} O_{2+} O_{3+} O_4

S_1= O_{1+} O_2

S_2= O_{3+} O_4

S_3= O_{1+} O_3

S_4= O_{2+} O_4

The actual number of pairs that falls into each of the four cells are then compared to the expected numbers if there was no relationship between closeness in distance and closeness in time. The expected number of pairs in each cell, under strict independence between distance and time interval, is obtained by the cross-products of the columns and rows total.

Table2: Expected logical structure of Knox Index

	Close in time	Not close in time
Close in distance	E_1	E_2
Not close in distance	E_3	E_4

where $E_1 = S_1 * S_3 / N$

$E_2 = S_1 * S_4 / N$

$E_3 = S_2 * S_3 / N$

$E_4 = S_2 * S_4 / N$

The difference between the actual (observed) number of pairs in each cell and the expected number is measured with a Chi-square statistic.

$$\chi^2 = \sum \frac{(O_i - E_i)^2}{Ei} \quad \text{with 1 degree of freedom....(1)}$$

"Close" time……: 2 years

"Close" distance……..: 70.962 km

Table3: Observed frequencies of Knox Index

	Close in time	Not close in time	
Close in distance	1867.831	1863.257	3731.088
Not close in distance	1028.130	1032.688	2060.818
	2895.961	2895.945	5791.906

Table 4: Expected frequencies of Knox Index

	Close in time	Not close in time	
Close in distance	1865.549	1865.538	3731.088
Not close in distance	1030.411	1030.406	2060.818
	2895.961	2895.945	5791.906

Monte Carlo Simulation of Critical Chi-square

Chi-square statistic associated with the usual probability test cannot be applied in this context, because the observations are not independent. When calculating the Chi-square statistic, interaction between space and time tend to be computed and it tends to get larger with increase sample size, a condition that would normally not be true with the independent observations. Monte Carlo simulation of the Chi-square value for the Knox Index under spatial randomness is used to handle the issue of interdependency (Dwass, 1957; Barnard, 1963). If the user selects a simulation, the routine randomly selects M pairs of a distance and a time interval where M is the number of pairs in the data set (M = N * [N-1]/2) and the Knox Index and the Chi-square test are calculated. Each pair of a distance and a time interval are selected from the range between the minimum and maximum values for distance and time interval in the dataset using a uniform random generator. The random simulation is repeated *K* times, where *K* is specified by the user.

The occurrence of the 12,595 cancer incidences month-wise were recorded in the database. The database was further broken down into six separate subsets according to year of occurrence. This database was a complete chronological data arranged according to the time, date and year of occurrence. Using the mean of both distance and time interval, the Knox Index was calculated for 12,595 cancer incidences, then using mean distance for the entire period, Knox Index is calculated for each year from 2001-2006. Table 5.3.5 presents the Chi-square and their pseudo-significance levels.

To minimize the error, 1000 random simulations were calculated for the incidences of cancer for the study period (2001-2006). An extreme value could be obtained by chance with a random distribution, hence, reasonable out-off points were selected from the limitation. The cut-off values were approximately taken as 1% and 5% significant levels.

Table 5: Knox Index for cancer incidences

Year	Actual Chi Square	95% Simulation Chi Square	Approximate p level
2001	2.63263	7.14580	Ns
2002	0.43504	13.31720	Ns
2003	9.76053	11.66386	Ns
2004	167.14952	7.35117	*
2005	0.66377	4.12694	Ns
2006	0.02180	12.63089	Ns
Overall	15.68842	54.71622	Ns

As Knox Index is a one-tailed test (i,e, only a high Chi-square value is indicated of spatial interaction), an upper threshold level of 95 percentile was adopted. Only if the observed Chi-square test for the Knox index is larger than 95 percentile, the null hypothesis of the random distribution between space and time will be rejected.

From the Table 5, it is observed that for the period of study there was no significant clustering between space and time. Around 16.5% of the incidences were both close in distance (i.e., close than the median distance interval between pairs of incidences) and close in time (i.e. close than the median time interval between pairs of incidences). However, when individual years are examined, only one year showed significant relationship i.e. 2004. The Knox Index is a simple measure of space – time clustering. The disadvantage with Knox Index is, it will produce different results for different cut-off points and incidences that cluster together spatially tend to cluster together temporally. To identify the clusters that occur over a short time period, the Mantel index was used.

Mantel Index

Mantel Index is a correlation between distance and time interval for pairs of incidents (Mantel, 1967) and resolves the problems of the Knox Index. It is a general test for the correlation between two *dissimilarity* matrices that summarizes comparisons between pairs of points (Mantel and Bailar, 1970). The test is based on a simple cross-product of two interval variables (e.g., distance and time interval):

$$T = \sum_{i=1}^{N} \sum_{j=1}^{N} (Xij - Mean\ X)(Yij - Mean\ Y) \quad \ldots\ldots(2)$$

where, X_{ij} is an index of similarity between two observations, i and j, for one variable (e.g., distance) while Y_{ij} is an index of similarity between the same two observations, i and j, for another variable (e.g., time interval). The cross-product is then normalized by dividing each deviation by its standard deviation:

$$r = \frac{1}{(N-1)} \sum_{i=1}^{N} \sum_{j=1}^{N} (Xij - Mean\ X)/sx * (Yij - Mean\ Y)/sy \quad \ldots\ldots(3)$$

$$= \sum_{i=1}^{N} \sum_{j=1}^{N} Z_x * Z_y / (-1)$$

Where Xij and Yij are the original variables for comparing two observations, i and j, and Zx and Zy are the normalized variables.

Mantel Index routine calculates the correlation between distance and time interval Table 6 examines the mantel correlation for the study period. It is seen that high correlation exists between the distances and time of incidences. In Knox Index only one year showed significance. If used as an index, rather than an estimate of variance explained, the Mantel Index can identify time periods when spatial interaction is occurring.

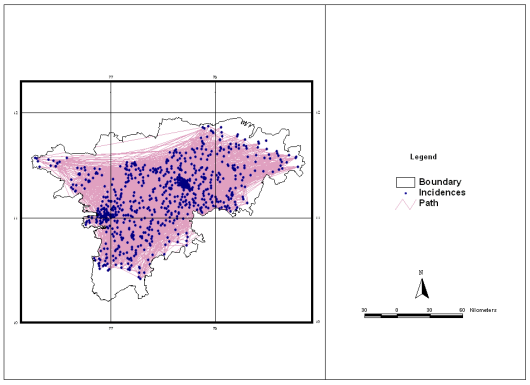
Monte Carlo Simulation of Confidence Intervals

Mantel Index is a Pearson product – moment correlation between distance and time interval, but, the measures are not independent and, in fact, are highly interdependent. Consequently, the usual significance test for a correlation coefficient is not appropriate. Instead, the mantel routine offers a simulation of the confidence intervals around the index. If the user selects a simulation, the routine randomly selects M pairs of a distance and a time interval where M is the number of pairs in the data set (M = N*[N-1]/2) and calculates the Mantel Index. 1000 random simulations were calculated for each year. An extreme value could be obtained by chance with a random distribution and reasonable cut-off points are usually selected from the simulation.

Mantel Index is a two tailed test (i.e., one could just as easily get dispersion between space and time as clustering), hence, we adopted a lower threshold of the 2.5% percentile and an upper threshold of 97.5% percentile. The null hypothesis of a random distribution between space and time is rejected only if the observed Mantel Index is smaller than the lower threshold or larger than the upper threshold. From Table 6 it was shown that all the time periods were significant except for the year 2004.

Spatial-Temporal Moving Average

Spatio-Temporal Moving Average is used for detecting changes in the behavior pattern of cancer incidences. It is a simple statistical method with moving mean center of *M* observations where *M* is a sub-set of the total sample, *N*. By 'moving', the observations are sequenced in order of occurrence and there is a time dimension associated with the sequence. The *M* observations are called the span and the default span is 5 observations. The span is centered on each observation so that there are an equal number on both sides. Since, there are no data points prior to the first event and after the last event, the first few mean centers will have fewer observations than the rest of the sequence. In brief, the Spatio-Temporal Moving Average simply plots the changes in the mean center of the span. Figure 3 show the movement of incidences in space and time for the 904 locations for a period of 72 months



.Figure 3: Moving path of the peak incidences in space and time

Table 6: Mantel Index for incidences of cancer from 2001 to 2006

Year	r	Simulation 2.5%	Simulation 97.5%	Approximate p-level
2001	0.01130	-0.01130	0.01558	*
2002	0.00570	-0.01450	0.01560	*
2003	0.01536	-0.01979	0.01730	*
2004	0.02839	-0.01687	0.01296	ns
2005	-0.00143	-0.02547	0.02172	*
2006	0.00357	-0.01208	0.01721	*
Overall	-0.00068	-0.00481	0.00714	*

Correlated Walk Analysis

(i) Analysis: Correlated Walk Analysis (CWA) is a tool to analyze the spatial and temporal sequencing of incidents. CWA routine makes guesses about the time and location of a next event, based on both the spatial distribution of the incidents and the temporal sequencing of them. It is a spatio-temporal moving average with a prediction of a next event. The difference between the first and second event is the first interval. The difference between the second and third event is the second interval. The difference between the third and fourth event is the third interval and so forth. For each successive interval, there is a time difference, there is a distance and there is a direction. This could be extended to all the intervals, comparing each interval with the next one; i.e., the first interval is compared with the second, the second interval with the third, the third interval with the fourth, and so on until the observed data were completed. When comparing successive intervals, this is called a *lag* of 1. Two events are required to create an interval. Thus, for a lag of 1, there are M=N-1 intervals where N is the number of events (e.g., for 3 incidents, there are 2 intervals). A lag of two compares every other event. The CWA- Correlogram routine calculates the Pearson Product – Moment correlation coefficient between successive events. Figure 4 represents the random walk model of the peak incidences with a start at Peelamedu and terminates near Pallatur.

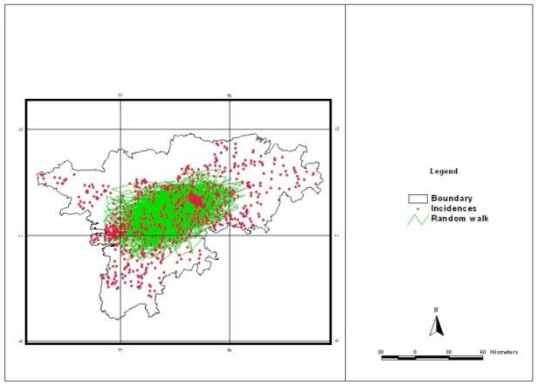


Figure 4: Random walk for cancer incidences

(ii) Diagnostics: The diagnostic analyst of CWA understands whether there are pattern in time, distance or direction. The diagnostics routine is similar to CWA – Correlogram except that it calculates an Ordinary Least squares auto regression for a particular lag. That is, it regresses each interval against a previous interval. This analyses the time interval, distance and bearing separately.

(iii) Prediction: CWA – prediction will help to make a guess about the next likely event, when it will occur and where it will occur. There are three methods for making a prediction, each with a separate lag:

(a)The *mean difference* applies the mean interval of the data for the specified lag to the last event. For example, for time interval and a lag of 1, the routine calculates the interval between each event and takes the average. It then applies the mean time interval to the last time in the data set as the prediction.

(b)The *median difference* applies the median interval of the data for the specified lag to the last event.

(c)The *regression equation* calculates a regression coefficient and constant for the specified lag and uses the data value for the last *interval* as input into the regression equation; the result is the predicted value. For the present study we have adopted the regression equation to predict the next event.

The routine takes the time and location of the last event and adds a time interval, a direction, and a distance as the predicted next event (next time, next location). Table 9 shows the predicted time, distance and bearing interval for the last case event 904 (observed) using the regression equation method for a lag distance of 1. For the above analysis, a lag distance of 1 was used and from the analysis the events were predicted for the next location and time at X=77.56946, and Y=11.05182 and 72.00176 months, respectively. A 3D elevation map is presented as Figure 5 for the spatio temporal distribution of cancer in the western part of Tamil Nadu which represents the predicted location of the predicted time of the next incidence occurrence. The regression analysis for space and time analysis where the multiple R2 = 0.00177 is presented in Table 7. The analysis of variance is presented as Table 8.

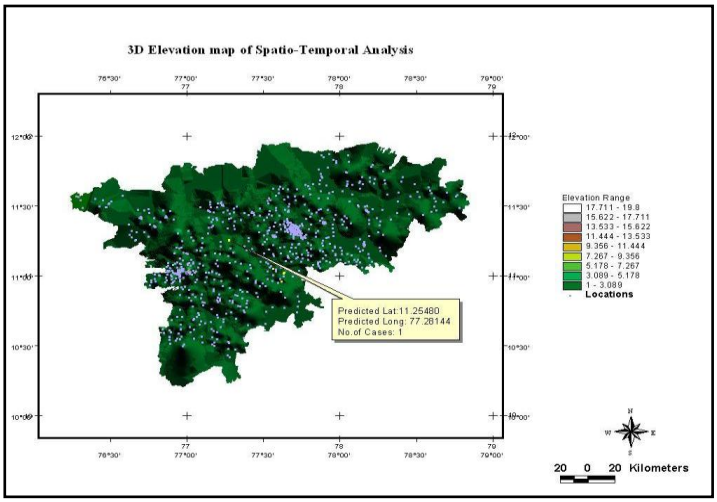


Figure 5: 3D Elevation map of spatial temporal analysis

Table 7: Regression analysis for space-time analysis

Variable:	Time	Standard error of estimate:		0.04197
Multiple R:	-0.00177	Squared multiple R:		0.00000
	Coefficient	Std error	t	P(2 Tail)
Constant	0.001767	0.00072	2.45310	0.01421
Lagged variable	-0.001767	0.01715	-0.10301	0.91796

Table 8: Analysis of variance

Source	**Sum of squares**	**df**	**Mean-square**	**F-ratio**	**P**
Regression	0.00002	1	20×10^{-6}	1061×10^{-5}	0.91795
Residual	5.98940	3401	176×10^{-5}	-	-
Total	5.98942	3402	-	-	-

Table.9:Table of predicted values

Variable	**Predicted value**	**From event**	**Method**	**Lag**
Time interval	0.00176	3409	Regression	1
Distance interval	67.125	3409	Regression	1
Bearing interval	102.32599	3409	Regression	1

IV. DISCUSSIONS AND CONCLUSIONS

Disease clustering studies seek to establish significant and unexpected elevated risks of a disease either in space or space and time. Such localized clusters could arise from many factors, for example unidentified causative agents (limb cancer), localized pollution (lung cancer), and common treatment side effects (radiotherapy). There are comprehensive specific methods available to reveal the above said problems and the recent one is Anderson and Titterington (1997). In general the disease cluster studies are performed to investigate:

(i) General tendency to cluster - pre-specified location or suspected hazards

(ii) Focused clustering - locations of putative hazard

Disease clustering studies may be used either for case event or aggregated data (Diggle and Elliott, 1995). To analyze the density of data points in space and time, traditional methods were used so far, which leads to insufficient conclusion. Therefore, space-time (spatio-temporal) model are adopted to overcome such problems. Models proposed by MacNab and Dean (2001) used temporal smoothing B-Splines and Congdon and Southhall (2005) accounted for temporal dependence using auto-regressive structure. For the present work, we have applied spatio-temporal model in geographical epidemiology using Crimestat III. This model is applied to taluk level cancer data from 2001-2006 with the aim to uncover the spatio and temporal patterns underlying the cancer data that could be interpreted with habitual diet/environment /hereditary in the western part of Tamil Nadu. Through this analysis we are able to pinpoint geographic areas with higher risk through exploratory spatial analyses, and to assess temporal variability of the risk surfaces, thus providing a working hypothesis on cancer. The model can improve upon the detection of hotspots when different diseases are highly associated with the same risk factors.

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