On the computational Bayesian survival spatial dengue hemorrhagic fever (DHF) modeling with double-exponential CAR frailty

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Abstract. In statistics, there are many types of data. Some data carry information about the location where observations occur, so that they can have a spatial effect. Dengue hemorrhagic fever (DHF) data which is easily transmitted, will be consequently has a spatial effect on its patient survival. In this study, we included DHF patient recovery time as a response variable, and several other variables as covariates considered to influence the patient's recovery time. Our aim in this study is to model how these variables affect the recovery rate for DHF patients with the accompanying patient residence as the spatial effects. Survival analysis is the best method for modeling the recovery rate for DHF patients. A conditional autoregressive (CAR) model is given to explain the relationship between adjacent locations, which is not explained in the general survival analysis. Several researchers have used the Cox model coupled with the Normal CAR. In this study, we used the Cox model using Normal CAR and compared it with the Double-Exponential (DE) CAR. To estimate the regression parameters of the Cox model, we used the Stan software. The advantage of Stan compared to the other Bayesian software such as BUGS and JAGS is the creativity of the researcher in writing the distribution as user-defined, as well as writing the CAR model in the Stan. Based on the WAIC value, modeling the DHF data using the Cox model coupled with the DE CAR is better than coupled with the Normal CAR. Based on the best model, variables that affect the recovery rate of DHF patients are age, the high school in last education, unemployed in the type of occupations, the stadium II in severity level, pulse, temperature, and leukocytes.

1. Introduction
Dengue hemorrhagic fever (DHF) is a disease caused by dengue virus from the genus Flavivirus, family Flaviviridae. Dengue virus is transmitted through the bite of the mosquito Aedes aegypti and Aedes albopictus [1]. Aedes aegypti mosquitoes spread the dengue virus through its bite. The virus can cause infections, ranging from subclinical infections to symptomatic infections [2]. Aedes aegypti and Aedes albopictus mosquitoes can live in tropical and subtropical countries, namely the Caribbean, South America, parts of Africa, Asia, and Australia as well as Oceania [3]. Some of the symptoms of DHF such as fever for 2-7 days accompanied by muscle aches, leukopenia, rashes, limfadenophathy, thrombocytopenia, and hemorrhagic diathesis [4]. According to the World Health Organization (WHO) data, Indonesia is the second country with the largest DHF case among the 30 countries endemic to the region [5]. In 2017 and 2018, East Java province was the second-highest DHF case in Indonesia after the West Java province. Surabaya city as the capital of East Java province has seen a decrease in DHF
cases in 2018. However, there are several sub-districts in Surabaya city with a high number of DHF cases. For this reason, it is necessary to prevent DHF cases in several sub-districts in the Surabaya city.

The response variable in this study is the time for the recovery of DHF patients (from entering the hospital until the DHF patients were declared cured). Based on the response variable, one of the statistical analysis methods used in this research is the survival analysis using the Cox model. DHF patient recovery time depends on where the patient lives. Thus, the survival data for DHF patients have spatial information. The addition of the random spatial effect on the survival model can overcome heterogeneity or sources of variance that cannot be explained by the model [5]. The spatial survival model with conditionally autoregressive (CAR) results the smaller errors and this CAR model can be a source of variance that cannot be explained in the general survival model [6]. In real data, modeling with the Normal CAR provides less precise results, and the use of a non-Gaussian CAR given better results [7].

One of the advantages of the Bayesian method over the frequentist method is its robustness in estimating small samples. Research conducted by [8] in the structural equation model, has shown that the Bayesian method with diffuse default priors becomes more biased when compared to the frequentist method, but with the correct priors, Bayesian is able to provide more accurate parameter estimates. Based on their systematic review, it can be concluded that Bayesian estimation can be used to solve small sample problems, thoughtful priors should be specified. On the other hand, the Bayesian method does not depend on asymptotic, a property that must be fulfilled when using the frequentist method in the context of a small sample [9]. Research conducted by [10] has shown that the Bayesian approach can provide more accurate estimates compared to the maximum likelihood estimation (MLE) for a small sample. Two real data examples had been provided to illustrate this method, namely the chipmunk example and the sunfish example. Those both data have a sample of 45 and 14, respectively. Furthermore, research conducted by [11] has compared several methods on a small sample. Some of the methods they compared are the Bayesian method with accurate prior information, the Bayesian method with diffuse priors, and the frequentist method: normal theory confidence limits, distribution of the product, and the percentile bootstrap. Bayesian methods with informative priors had the most powerful. Thus, Bayesian methods have the potential for increasing power in the analysis. Research on the bootstrap method carried out by [12] has compared the Bayesian bootstrap with the standard bootstrap. They succeeded to demonstrate that the Bayesian bootstrap provides uncertainty intervals that are more reliable than those from the standard bootstrap. One of the studies in the scope of time series analysis using the Bayesian method has been conducted by [13]. In his research, he has compared the performance of small samples, namely \( n = 1, 3, 5, 10, \) and 15 for the Bayesian multivariate vector autoregressive (BVAR-SEM) time series model relative to frequentist power and parameter estimation bias. The result obtained was that the Bayesian approach provided an increased sensitivity for hypothesis testing.

Based on the explanation above, it is necessary to model the recovery time of DHF patients. To be able the modeling will be given several covariates that are considered influencing the recovery time of DHF patients. By using the Cox regression model, parameter estimation was carried out using the Bayesian method. The Bayesian method that we have chosen is the Hamiltonian Monte Carlo (HMC) and we used Stan software. Stan is a very expresssive programming language for statistical model specifications [14]. Bayesian inference is carried out using the HMC to obtain parameter estimates from the posterior. Compared to Gibbs and Metropolis samplers, HMC is more efficient and robust [15]. Thus, it is possible to estimate more complex models such as the Normal CAR and Double-Exponential (DE) CAR model. The history of HMC and comparison of its performance with Markov chain Monte Carlo (MCMC) can be seen in Monnahan [16]. As researchers, using Stan is a convenience, because we can easily define models as user-defined. To add a model or distribution in Stan can be seen in Annis [17].

2. Method
2.1 Survival Spatial Model
The Cox model is often used for analyzing the survival data. This model can be written as Equation (1)
\[ h(t,x) = h_0(t) \exp(\beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p), \]  

(1)

where \( h_0(t) \) is the baseline hazard, \((x_1, x_2, \ldots, x_p)\) is the \(p\)-vector predictor variables, and \((\beta_1, \beta_2, \ldots, \beta_p)\) is the \(p\)-vector estimator regression parameters of the Cox model. If the survival data contains information about spatial aspects, then the Cox model can be added by the spatial random effects. To test whether the data has a spatial correlation or not, the Moran’s I value can be used. The value of Moran’s I would be in between \(-1\) and \(1\) and it can be interpreted as 

a. When it is getting closer to \(1\), the locations have a stronger spatial autocorrelation positively,

b. When it approaches \(0\), there is no spatial autocorrelation among locations,

c. When it comes close to \(-1\), the locations have increasingly negative spatial autocorrelation.

2.2 Survival Spatial Model

If there is a spatial correlation, then the Cox model in Equation (1) with added spatial effects can be written in Equation (2).

\[ h(t_i, x_i) = h_0(t_i) \exp(\beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_p x_{ip} + \phi_i), \]  

(2)

where \(\phi_i\) is the spatial random effect for \(i\)-th individual. Random effects in the spatial survival model are often given by prior CAR [18,19]. Most researchers have used Normal CAR to provide spatial random effects on survival data. However, [7] had developed a non-Gaussian CAR. In their study, Normal CAR was compared to Double-Exponential CAR. The estimation was carried out using the Bayesian Markov chain Monte Carlo (MCMC) method which is implemented in the BUGS (Bayesian inference Using Gibbs Sampling) software. In our study, we used Hamiltonian Monte Carlo (HMC) implemented in the Stan software. By using the concept of physics theory, the HMC algorithm was proposed by [20]. HMC is a family of the MCMC algorithm, but it claims more efficient than the MCMC in BUGS because of two reasons [16]. First, HMC requires precise gradients and the second is the original HMC algorithm requires expert, hands-on tuning to be efficient [21]. A complete mathematical explanation for the HMC algorithm can be studied in Gelman, et al. [22].

3. Result and Discussion

3.1 Data Collection

In this study, we collected data from the Dr. Soetomo hospital in Surabaya city through medical record data. This dataset collected from January 2016 until December 2019 and obtained 21 DHF cases in eastern Surabaya. This dataset contains a response variable, covariates, and spatial information that can be seen in Table 1. The response variable in this study is the time duration of DHF patients’ stays in the hospital include its censoring indicator. Several covariates considered to influence the patient’s recovery time are gender, age, last education, type of occupations, stadium, fever days before entering the hospital, temperature, pulse, respiratory rate, haemoglobin, haematocrit, leukocytes, and platelets. Spatial information in this study is the sub-district in eastern Surabaya where the patients live. The number of cases for each sub-district in eastern Surabaya can be seen in Figure 1. As has been stated in the Introduction section, several studies have shown the advantages of the Bayesian method for small sample problems. According to the new studies (conducted over a period of 10 years) conducted by [8-13], small samples can still be analyzed using the Bayesian method. The data in this study is quite limited, but the assurance of the Bayesian method with the correct prior selection in this study has been implemented and has been able to provide analysis results as additional evidence of all research support with small samples in the literature review in the first section.
Table 1. Research variables DHF cases in eastern Surabaya and their description

| Symbol | Information of Variables | Unit or value |
|--------|--------------------------|---------------|
| $t$    | The duration of patients to meet recovery event | Days |
| $\delta$ | The indicator of censored data | (1: uncensored; 0: censored) |
| $X_1$ | Gender | (1: female; 0: male) |
| $X_2$ | Age | Years |
| $X_3$ | Last education | (1: high schools; 2: universities; 3: others (base)) |
| $X_4$ | Types of occupations | (1: public servants; 2: private employees; 3: unemployed; 4: housewife (base)) |
| $X_5$ | DHF stadium | (1: stadium-I (base), 2: stadium-II, 3: stadium-III) |
| $X_6$ | Fever days before entering the hospital | Days |
| $X_7$ | Pulse | Times/minute |
| $X_8$ | Respiratory | Times/minute |
| $X_9$ | Temperature | Celsius |
| $X_{10}$ | Haemoglobin | g/dL |
| $X_{11}$ | Haematocrit | % |
| $X_{12}$ | Leukocytes | $10^3$/uL |
| $X_{13}$ | Platelets | $10^3$/uL |
| $S$ | Sub-district | (1: Tenggilis Mejoyo (TM), 2: Gunung Anyar (GA), 3: Rungkut (R), 4: Sukolilo (S), 5: Mulyorejo (M), 6: Gubeng (G), 7: Tambaksari (T)) |

Based on Figure 1, we can see that Gubeng and Tambaksari are the sub-districts with the highest cases, while Gunung Anyar and Rungkut are the sub-districts with the lowest cases. By using the queen contiguity method, the list of neighbours of each sub-district in eastern Surabaya can be seen in Figure 2, where TM, GA, R, S, M, G, and T are the codes for each sub-district as in the last line of Table 1. The
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explanation for Figure 2 is as follows: the first line is the list of neighbours for Tenggilis Mejoyo sub-district, the second line is the list of neighbours for Gunung Anyar sub-district, and so on.

3.2. Double-Exponential Conditionally Autoregressive in Stan

For modeling certain data using the CAR model, the most researcher has chosen the Normal CAR. However, choosing the Normal CAR is not always entirely appropriate, especially for thick-tailed data [7]. The alternative to this problem is to use an exponential family distribution. In this study, we propose the Double-Exponential (DE) or Laplace CAR in Stan. Based on the fact that the tail of the Double-Exponential distribution is heavier than the Normal distribution [23]. The DE CAR model is more robust than the Normal CAR model [23].

Let \( \phi = (\phi_1, \phi_2, \ldots, \phi_S)^T \) is the spatial random variable that follows a DE CAR distribution, where \( S \) is the number of sub-areas in an area. The corresponding conditional distribution specification is in Equation (3)

\[
p(\phi_i | \phi_j, j \neq i, \tau_i^{-1}) = \text{DE} \left( \frac{1}{d_{ij}} \right) .
\]  
(3)

Their joint distribution simplifies to Equation (4)

\[
\phi \sim \text{DE}_n \left( 0, \tau (\mathbf{D} - \mathbf{W})^{-1} \right).
\]  
(4)

where \( \text{DE}_n \) denotes the \( n \)-dimensional DE distribution, \( \mathbf{D} \) is an \( n \times n \) diagonal matrix where each diagonal entry \( d_{ii} \) contains the number of neighbours of the area \( R_i \) and all off-diagonal entries are zero, \( \mathbf{W} \) is the adjacency matrix where entry \( w_{ij} = 1 \) if areas \( R_i \) and \( R_j \) are neighbours and \( w_{ij} = 0 \) otherwise and all diagonal entries \( w_{ii} \) are zero. We set \( \tau \) in Equation (3) equal to 1 then it can be explained below:

\[
\phi \sim \text{DE}_n \left( 0, (\mathbf{D} - \mathbf{W})^{-1} \right) \text{ with probability density function (p.d.f.) as Equation (5) [24]}
\]

\[
p(\phi) = \frac{2}{(2\pi)^{S/2} \left| (\mathbf{D} - \mathbf{W}) \right|^{1/2}} \exp \left( -\sqrt{2\phi' (\mathbf{D} - \mathbf{W}) \phi} \right) \frac{\pi}{2^{S/2-1}} \left( \frac{\pi}{2} \right)^{S/2} \left( \frac{\phi' (\mathbf{D} - \mathbf{W}) \phi}{2} \right)^{1/2} .
\]  
(5)

Equation (5) can be explained as below

\begin{align*}
\text{Figure 2.} & \text{ List of neighbours in each sub-district in eastern Surabaya}
\end{align*}
\[
p(\phi) = \frac{2}{(2\pi)^{n/2}} \left( \frac{\pi}{2} \right)^{1/2} \left( \frac{1}{2} \right)^{1/4} \left( \phi^T (D - W) \phi \right)^{-1/4} \exp \left( -\sqrt{2} \left( \phi^T (D - W) \phi \right)^{1/2} \right)
\]

Because
\[
\frac{2}{(2\pi)^{n/2}} \left( \frac{\pi}{2} \right)^{1/2} \left( \frac{1}{2} \right)^{1/4} \left( \phi^T (D - W) \phi \right)^{-1/4} \exp \left( -\sqrt{2} \left( \phi^T (D - W) \phi \right)^{1/2} \right)
\]
is a constant so that p.d.f. can be rewritten as Equation (6)
\[
p(\phi) \propto \left( \phi^T (D - W) \phi \right)^{-1/4} \exp \left( -\sqrt{2} \left( \phi^T (D - W) \phi \right)^{1/2} \right).
\]

Then the log density as in Equation (7).
\[
\log \left( p(\phi) \right) = \left( (S+1)/4 \right) \log \left( \phi^T (D - W) \phi \right) - \sqrt{2} \left( \phi^T (D - W) \phi \right)^{1/2}.
\]

According to the concept of writing the CAR distribution into a form of pairwise difference formulation by [14], Equation (7) can be rewritten as Equation (8) to be used in Stan.
\[
\log \left( p(\phi) \right) = \left( (S+1)/4 \right) \log \left( \sum_{i,j} (\phi_i - \phi_j)^2 \right) - \sqrt{2} \left( \sum_{i,j} (\phi_i - \phi_j)^2 \right)^{1/2}.
\]

Based on Equation (8), the Stan code for DE CAR can be seen in Syntax 1.

```stan
functions{
  real car_double_exponential_lpdf( vector phi, int S, int[] node1, int[] node2 ) {
    real m;
    m = 0.25 * (S + 1);
    return m * log(dot_self(phi[node1] - phi[node2])) -
      (2^0.5) * (dot_self(phi[node1] - phi[node2]))^0.5 +
      double_exponential_lpdf(sum(phi) | 0, 0.001 * S);
  }
}
```

Syntax 1. A user-defined Stan code for DE CAR

3.3. Choosing the Best Model

Based on the Kolmogorov-Smirnov test with the significance level \( \alpha = 5\% \), eastern Surabaya DHF data follows the Weibull distribution. Then, the Moran’s I value obtained for eastern Surabaya DHF data is 0.407738. This number is enough to support that the data has a spatial correlation, because the data available is only 21 cases. Using the Weibull distribution, we tried to compare the Cox model with the Normal CAR and Cox model with the DE CAR. The user defined Stan code for Normal CAR has been explained and written by [14], while in this study we provided an explanation of DE CAR and its Stan user-defined code as seen in Syntax 1. Both models are estimated by using Bayesian HMC with Stan. Before determined the significance of the parameters, the WAIC of the two models will be calculated, respectively. The model having the smallest WAIC is the best. Table 2 shows the comparison of WAIC.
for both models. Based on the WAIC value in Table 2, the model with the DE CAR is better than the model with the Normal CAR. Then, the determination of the significance of the parameters and calculation of the recovery rate will be based on the model with the DE CAR as the best model.

Table 2. WAIC value for the Cox model with the Normal CAR compared to the Cox model with the DE CAR

| Survival spatial model using Weibull distribution | WAIC |
|--------------------------------------------------|------|
| with Normal CAR                                  | 71.6 |
| with DE CAR                                      | 71.3 |

3.4. Estimation and Analysis Based on the Best Model

Based on the previous sub-section, as the selected best model, the parameter estimation, therefore, is performed for the model with the DE CAR. Table 3 shows the results of the estimated parameters. All parameter estimates have met the convergence requirement, namely that the Rhat value has been perfectly worth 1.0 [25]. To make it easier to see the resulting model, significant parameters are marked with a gray shading, that is, according to the criteria, the zero value is not within the 95% credible interval.

Table 3. Estimation parameters result of Weibull Cox model with DE CAR

| Estimator  | Mean   | 2.5%    | 97.5%   | Rhat | Estimator  | Mean   | 2.5%    | 97.5%   | Rhat |
|------------|--------|---------|---------|------|------------|--------|---------|---------|------|
| $b_0$      | 0.7963 | -0.0865 | 1.6985  | 1    | $b_1$      | -0.1747| -0.3581 | 0.0027  | 1    |
| $b_1$      | 0.2768 | -0.1514 | 0.7009  | 1    | $b_2$      | 0.0359 | 0.0191  | 0.0524  | 1    |
| $b_{2,1}$  | 0.0158 | 0.0040  | 0.0273  | 1    | $b_3$      | -0.0656| -0.1500 | 0.0180  | 1    |
| $b_{3,1}$  | -0.8290| -1.4311 | -0.2347 | 1    | $b_y$      | -0.2142| -0.2618 | -0.1659 | 1    |
| $b_{3,2}$  | 0.2036 | -0.4628 | 0.8547  | 1    | $b_{1,3}$  | 0.0155 | -0.0619 | 0.0954  | 1    |
| $b_{4,1}$  | 0.3056 | -0.1936 | 0.7928  | 1    | $b_{1,1}$  | 0.0072 | -0.0348 | 0.0482  | 1    |
| $b_{4,2}$  | -0.1483| -0.6018 | 0.3150  | 1    | $b_{2,3}$  | 0.1351 | 0.0589  | 0.2104  | 1    |
| $b_{4,3}$  | -0.6865| -1.2429 | -0.1287 | 1    | $b_{1,1}$  | -0.0011| -0.0065 | 0.0041  | 1    |
| $b_{5,1}$  | -1.1497| -1.5866| -0.7183 | 1    | $\rho$     | 3.5318 | 3.0714  | 4.0356  | 1    |
| $b_{5,2}$  | -0.2428| -1.1819 | 0.6849  | 1    |            |        |         |         |      |

Based on Table 3, factors that significantly affect the recovery rate of DHF patients in eastern Surabaya are age, the high schools in last education, unemployed in the type of occupations, the stadium II in severity level, pulse, temperature, and leukocytes. Then, the Weibull Cox model with DE CAR spatial effect can be written as Equation (9) [6].

$$h(t, x) = 3.5318^{t_{2.5318}} \exp(0.7963 + 0.0158x_{2,1} - 0.8290x_{3,1} - 0.6865x_{4,1} - 1.1497x_{5,1} - 0.2142x_{6,1} + 0.0359x_{6,1} + 0.1351x_{6,1} + \phi).$$  

4. Conclusion

This study has successfully demonstrated the performance of Cox modeling with its combination and comparison using Normal CAR and DE CAR. Based on the WAIC value, the Cox model with DE CAR is better for representing the survival pattern of eastern Surabaya DHF patients compared to Normal CAR. This shows that these data support the fact that DE CAR is more robust than Normal CAR. It opens the way that non-Gaussian CARs will be more willingly used in modeling data containing spatial information. Another main result is the finding of factors that have a significant effect on the recovery rate for DHF patients in eastern Surabaya, namely age, the high schools in last education, unemployed in the type of occupations, the stadium II in severity level, pulse, temperature, and leukocytes. There are
two groups of factors that influence the response, namely the positive and negative coefficients in the Cox model. Several factors, namely age, pulse, and leukocytes have a positive coefficient. This means that increasing the value of these factors will accelerate the recovery rate for DHF patients. Other factors, namely high schools in the last education, unemployed in the type of occupations, the stadium II in severity level, and temperature have a negative coefficient. This means that the acceleration of the patient's recovery rate will be slower if the value of these factors increases.

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