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Research Article

Numerical Study on Zika Epidemic Early Warning Algorithms Driven by Dynamical Network Biomarker

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This paper focuses on the numerical study and precise forecast of Zika epidemic. An early warning index algorithm of Zika epidemic is given, and the applications of this algorithm are investigated. We pay attention to the mathematical approaches to estimate the tendency of Zika epidemic in detail. A numerical experiment is provided to illustrate the effectiveness of the proposed method by the numerical calculation of early warning index of Brazil.

1. Introduction

Nowadays, the forecast has played an important role in the theory and application of epidemic, especially in the research of the effective measures before the outbreak of the epidemic. Numerical computation is becoming the center position in the investigations of epidemic tendency which describes many natural phenomena, for example, in meteorology and biology [1–10]. However, we mainly concern the reliability and feasibility of numerical simulations by the network biomarker of Zika virus.

This work is motivated for two facts. Firstly, some relative works have been finished. Lesterhuis W.J. and his team had made useful contributions to the discovery of the threshold value in the system by the compare of dynamical and static network biomarker in the complex disease [11]. The results of Dahlem M.A. show that the critical condition of the disease will be rapidly transformed into the illness state motivated by some factors, and the threshold value can be viewed as early warning signal of some complex disease [12]. Chen L.N. utilized dynamical network biomarker (DNB) to analyze the dynamical signal of the disease and provide three common characters of DNB [13]. These results are the foundations of forecast and numerical simulations by DNB. Secondly, a high degree of concern on Zika virus has been aroused in the world. As we know, Zika disease is a very serious epidemic which is a self-limited acute infectious disease and is mainly caused by Aedes mosquitoes. For example, at least 11000 confirmed cases of Zika have affected pregnant women, which leads to about 10000 cases of birth defects, such as microcephaly. The clinical features are mainly rash, fever, joint pain, or conjunctivitis, and it rarely causes death. Works on Zika continue to be an interesting topic. The results have illustrated that Zika virus has no protein structure (NS1) which is most related to the outbreak of Zika disease [14]. To the best of our knowledge, no investigations of the numerical computations of Zika virus protein in a finite time interval exist in the literature [6–10].

In this work, we mainly focus on the early warning forecast of Zika by DNB. The protein of Zika virus is used to construct DNB, and the early warning index is also established by the property of DNB molecule. The early warning model is defined so that we can distinguish the critical value of Zika epidemic outbreak. The data is obtained by some country on Zika virus. In the numerical experiments, the method is applied to compute the year of Zika epidemic outbreak in one country, and the results show that it matches well with the time of Zika epidemic real outbreak in that country. And the results demonstrate that under certain appropriate assumptions the early warning index algorithm is well designed so that it can forecast the critical time exactly.

The rest of this paper is organized as follows. Section 2 deals with some preliminaries. In Section 3 the theoretical results of the early warning algorithm are summarized. Section 4 presents the details of the numerical implementations. Illustrative numerical experiments for the main results are included in Section 4. We demonstrate that the main theorem and numerical implementation methods can be applied to Brazil Zika forecast. Finally, Section 5 is addressed to summarize the conclusions of the paper.

2. Preliminaries

2.1. Results on the Protein of Zika Virus. Zika disease is highly contagious and is frequently found all over the world. Up to now, many advanced researches have been pursued in different aspects. Recently, the results in [14] show that the molecular structure of nonstructural protein, that is, NS2B, which is related to the outbreak of Zika epidemic, is the foundation of Zika virus research.

2.2. Resource of the Data. The data in this paper is selected from the Zika protein data in Brazil and United States, and they are shown on the internet website(https://www.ncbi.nlm.nih.gov/) As we know, Zika virus is single chain RNA virus, and more than 10000 basic groups encode into ten proteins. There are seven nonstructural proteins, such as NS2B, NS2A, NS4A, NS4B, NS1, NS3, and NS5, and three structural proteins, such as C proteins, PRM, and E protein.

3. Design of the Early Warning Algorithm

3.1. A Selected Example. Here we choose NB2B protein as an example. Suppose that this protein is contained as t chains, which is denoted as $p = x_1, x_2, \ldots, x_t$, where $i = 1, 2, \ldots, t$. $x_i \in \{A, V, L, I, P, F, W, M, D, E, G, S, T, C, Y, N, Q, R, K, H\}$. Assume that one country reports m kind Zika virus proteins in the $(y-1)$-th year, whose amino acid series are $P_{y-1,1}, P_{y-1,2}, \ldots, P_{y-1,m}$.

And it reports m kind Zika virus proteins in the y-th year, whose amino acid series are $P_{y,1}, P_{y,2}, \ldots, P_{y,n}$. The number of amino acid P_{ij} is denoted as C_{ij}, where $i = y-1, y$, $j = 1, 2, \ldots, k$, and $k = \max\{m, n\}$. We choose k-th amino acid in turns from the sequences $P_{y-1,1}, P_{y-1,2}, \ldots, P_{y-1,m}$ and resemble them as a new series in the older turn $L_{y-1,k}$. Furthermore, we choose the amino acid to be denoted as x_k which appears most frequently, where $k = 1, 2, \ldots, r$, $r = \max\{C_{y-1,1}, C_{y-1,2}, \ldots, C_{y-1,m}\}$; otherwise, the first will be selected. Then x_k will be interlinked in turns and to obtain a new amino acid series $L_{y-1} = x_1 x_2 \ldots x_k$.

Therefore, it can be compared with the series $P_{y,1}, P_{y,2}, \ldots, P_{y,n}$ successively, and the results can be shown as follows. If the condition $r > C_{y,j}$ holds, we compare before $C_{y,j}$ amino acid of the series L_{y-1} with every series of y-th year. If the condition $r \le C_{y,j}$ holds, we compare before r amino acid of $P_{y,j}$ with the series L_{y-1}. If the kind of these amino acids is the same, then it is assigned as 1; otherwise, it is assigned as 0. Therefore, we can obtain a new series of y-th year which has only the elements 0 and 1 and can be denoted as $Q_{y,1}, Q_{y,2}, \ldots, Q_{y,n}$.

3.2. Implementations of EWI Algorithm. Now we compute the following quantities.

Step 1. The y-th year arithmetic mean value A_y is shown as follows.

$$A_y = \frac{1}{n}\sum_{j=1}^{n} f(y, j) \tag{1}$$

The standard deviation STD_y is defined as

$$STD_y = \sqrt{\frac{\sum_{j=1}^{n}\left(f(y, j) - A_y\right)^2}{n}}, \tag{2}$$

and the coefficient of variation CV_y is defined as

$$CV_y = \frac{STD_y}{A_y}, \tag{3}$$

where $f(y, j)$ denotes the number of times of one appearing in Q_{ij}, $j = 1, 2, \ldots, n$. The value of the parameters A_y, STD_y, and CV_y of other proteins is obtained by the same method.

Meanwhile, we utilize the software SAS to test on all protein standard deviations in all considered years, and we choose the protein as the central, which shows obvious difference; that is, it is can be seen as the signal of dynamical network biomarker, and others can be defined as noncentral protein.

As we know, every series contains N kind amino acids so that the times which every amino acid emerges in the y-th year can be calculated. And the result is as follows.

Step 2.

$$F_{x_i} = \frac{1}{n}\sum_{j=1}^{n} f_{x_i}(y, j), \tag{4}$$

where $f_{x_i}(y, j)$ denotes the times which x_i emerges in the amino acid $P_{y,j}$.

Following from the above results, we can obtain a feature vector of amino acid $V(y)$, and feature vectors of other amino acids are obtained by the similar method [15].

Step 3. The matrix of feature vector is defined as

$$V = \left[V_1(y), V_2(y), \ldots, V_N(y)\right], \tag{5}$$

where $V_k(y)$ is the feature vector of the k-th protein, $k = 1, 2, \ldots, N$. And the feature distance of protein in the y-th year is defined as follows:

$$ED_{k_1 k_2} = \sqrt{\left(A_{k_1} - A_{k_2}\right)^2 + \cdots + \left(F_{k_1 x_N} - F_{k_2 x_N}\right)^2}, \tag{6}$$

where k_1, k_2 denote two kinds of different proteins. Therefore, we can compute all feature distances between N kinds of protein.

Table 1: Summaries of Zika virus EWI from 1980 to 2016 in Brazil.

Year	EWI	Year	EWI	Year	EWI
1980	0.011234	1992	0.881891	2005	0.889432
1981	0.201478	1993	0.967212	2006	0.543217
1982	0.310231	1994	0.043254	2007	0.612523
1983	0.711321	1995	0.006547	2008	0.321876
1984	0.781221	1996	0.054334	2009	6.342679
1985	0.219911	1997	0.063429	2010	0.546751
1986	0.097215	1998	0.033459	2011	0.132156
1987	0.021018	1999	0.207752	2012	0.923995
1988	0.034662	2000	0.304561	2013	0.992189
1989	0.800772	2001	0.762337	2014	3.032341
1990	0.821221	2002	0.821356	2015	7.127854
1991	0.940983	2003	0.021355	2016	4.452137

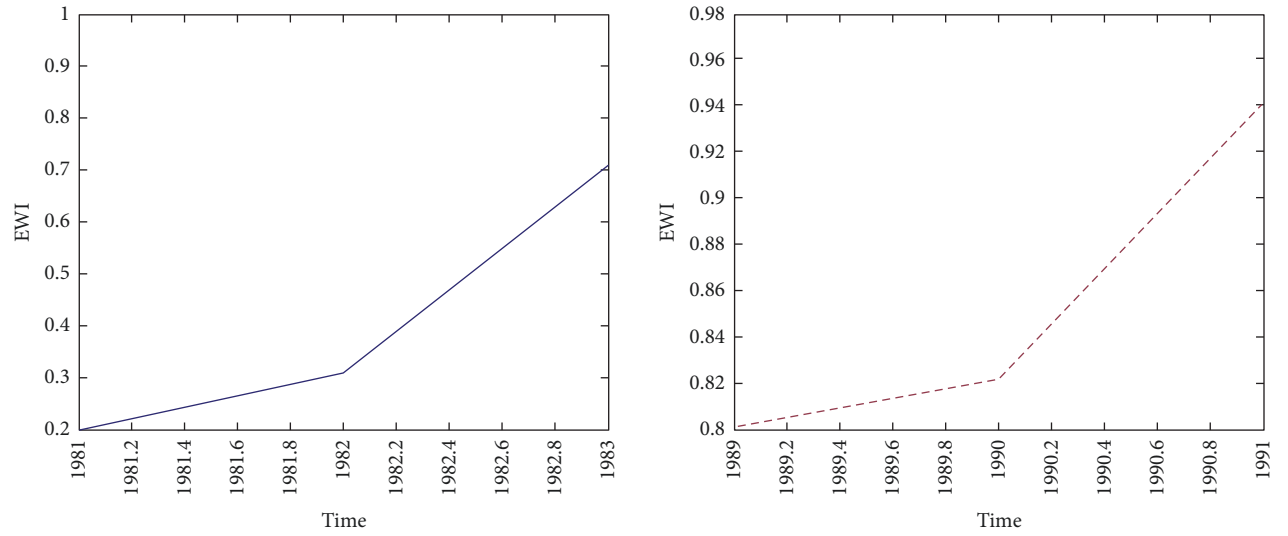

Figure 1: Variation tendency of EWI in Brazil in the time intervals [1981, 1983] and [1989, 1991].

By the dynamical property of center protein and DBN, Early Warning Index (EWI) can be computed as follows.

Step 4.

$$EWI = \frac{\overline{CV_0} \bullet \overline{ED_0}}{ED_0}, \tag{7}$$

where $\overline{CV_0}$ denotes the mean value of the coefficient of variation of Zika virus center protein, $\overline{ED_0}$ denotes the mean character distance of center proteins, and ED_0 denotes the mean character distance of center proteins and noncenter proteins.

We can apply EWI to determine the outbreak time of Zika epidemic as follows.

Step 5. If the following conditions are satisfied,

$$\begin{aligned} EWI_{y-1} &< 1, \\ EWI_{y+1} &> 1 \\ EWI_y - EWI_{y-1} &< EWI_{y+1} - EWI_y, \end{aligned} \tag{8}$$

then the y-th year is called as the critical year of Zika epidemic outbreak, and the $y+1$-th year is called the year of Zika epidemic outbreak, where EWI_{y-1}, EWI_y, and EWI_{y+1} are EWI of the $y-1$-th, y-th, and $y+1$-th year, respectively [16, 17].

4. Applications of EWI Algorithm

This section is the applications of EWI algorithm. We apply the data from Brazil in the past 37 years. The change is analysed and the precise forecast is obtained.

4.1. EWI of Zika Epidemic in Brazil. Here we select the data of ten kinds of proteins of Zika virus from 1980 to 2016. By the former formula, we can calculate EWI of Brazil, and the results are shown as Table 1 [17, 18].

4.2. Analysis on Early Warning Model of Brazil Zika Epidemic. As can be seen from Figure 1, the value of EWI in the years 1983 and 1991 increases suddenly. However, $\mathrm{EWI}_{1982} < 1$, and $\mathrm{EWI}_{1983} < 1$. It follows from EWI algorithm that there were

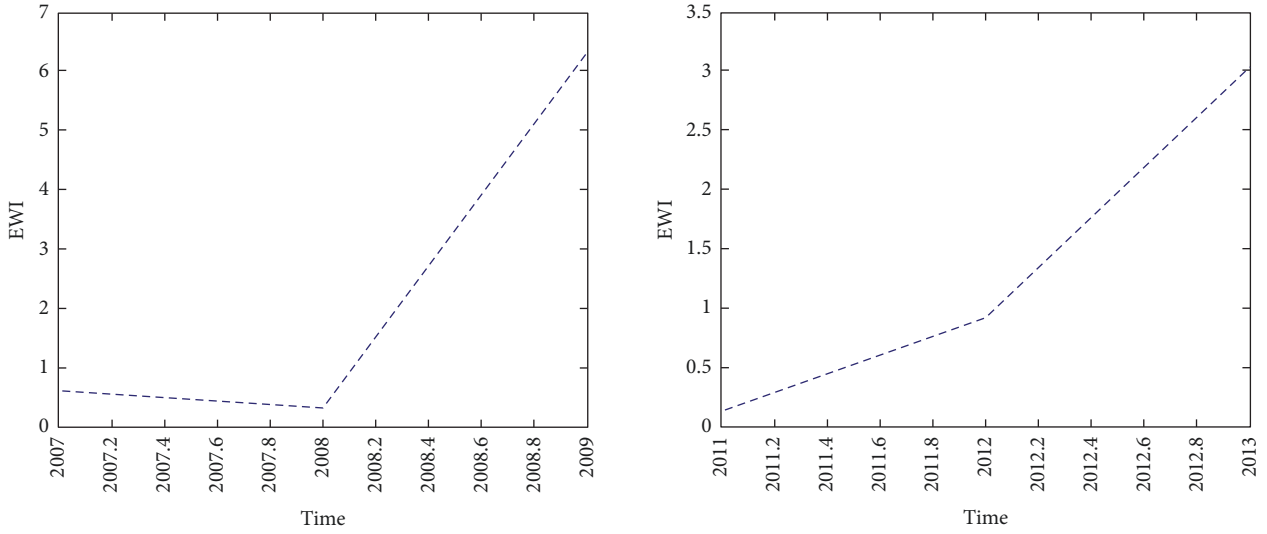

Figure 2: Variation tendency of EWI in Brazil in the time intervals [2007, 2009] and [2011, 2013].

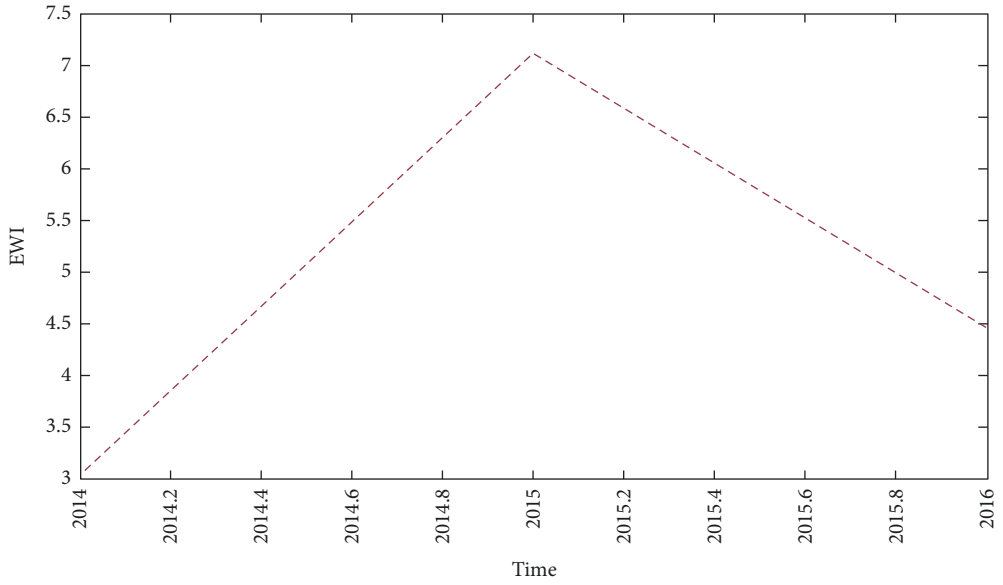

Figure 3: Variation tendency of EWI in Brazil from 2014 to 2016.

no Zika epidemics in Brazil at that time. This theoretical result matches the reality well.

As can be seen from these numerical results shown as Figures 2 and 3, in the years 2009 and 2014 EWI increased suddenly and it is obviously greater than the former. For example, $EWI_{2013} < 1$, while $EWI_{2014} > 1$. It follows from EWI algorithm that there were Zika epidemics in Brazil at that time. Therefore, the years 2009 and 2014 are called the years of Zika epidemic outbreak, and the years 2008 and 2013 are called the critical years of Zika epidemic outbreak. These theoretical results match the reality well. The numerically detected behavior of the system indeed reflects its real fact which can be described more accurately.

4.3. Forecast on Zika Epidemic in Brazil. Based on these numerical results, we can predict Zika epidemic in the near future in Brazil. As can be seen from these numerical results shown as Figures 2 and 3, in the year 2017, EWI maintains steadiness and does not increase suddenly and it is not obviously greater than the former. That is, $EWI_{2017} < EWI_{2016}$. If $EWI_{2018} > EWI_{2017}$ or $EWI_{2019} > EWI_{2017}$, it follows from EWI algorithm that there will be Zika epidemic in Brazil at that time. Otherwise, i.e., $EWI_{2018} < EWI_{2017}$ and $EWI_{2019} < EWI_{2017}$, and Zika epidemic will not break out in 2018 and 2019.

4.4. Comparison with Other Models and Methods. As we know, some existing work about this topic is also interesting,

such as References [19, 20]. These studies used ecological niche models (ENMs) to map the possible distribution of Zika virus, utilizing a different combination of occurrence data, environmental predictors, and statistical approaches. And it is shown in [20] that the results obtained by generic and uniformed stochastic county-level simulations illustrate a basic consensus method, which can resolve conflicting models of potential outbreak geography and seasonality in the United States. However, our results illustrate that the forecast of the outbreak of Zika by dynamical network biomarker relies on the protein of Zika virus, and the early warning index is also established by the property of DNB molecule. This is to say, our method mainly depends on dynamical network biomarker, such that it can be less influenced by uncertain factors. The method in [20] focuses on the United States as a test system and depends on many random factors, including environmental variable and population-at-risk. Therefore, we have the same purpose, i.e., to forecast the outbreak of Zika epidemic, but by different methods.

5. Conclusion

The main result of this paper is the construction and applications of Zika epidemic EWI algorithm. It focuses on the mathematical approaches to estimate the tendency of Brazil Zika epidemic in the past 37 years. The results show that the methods are effective and the numerical experiments are performed and match the results of theoretical analysis. More simple and higher accuracy methods will be shown in our further work.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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