A Dynamic Drug Delivery System Based on the Ebola Outbreak

Abstract

Nowadays, fighting against Ebola has become a heated discussion around the world. In our paper, we build a model which focuses on the spread of Ebola and the design of a delivery system. The whole delivery system includes the speculation of manufacturing speed, the selection of locations and quantities of medicine that needed.

In the first step, based on the classic S-E-I-R-S model, we creatively build a more realistic model which is consistent with features of Ebola. We have considered 8 factors and use the Simulink Design Optimization of MATLAB to fit parameters in the differential equation set. According to our analysis, the effective contacts rate is a key factor to evaluate the spread speed of Ebola. We predict the effective contacts rate in other countries based on the BP neutral network. Therefore, according to basic assumptions, we obtain the quantity of medicine that needed.

In our second step, we study on the speed of manufacturing medicine. We creatively adopt the classic Logistic growth model and analyze the rationality of it in theory. Then, we plot speculating curves for manufacturing speed of 4 producing countries.

In our third step, we divide the whole process into two phases: demand exceeds supply and supply exceeds demand. We design delivery strategies respectively. We divide the whole affected area into 14 smaller regions. We set 10 days as a delivery period and deem the whole process as a discrete dynamic process. By adding some restrictions, we transfer it into a NLP problem which belongs to optimal problems, and we find the local optimal solution. In the model test section, we give a specific example respectively in two phases to illustrate.

We process the sensitivity analysis on our method. We draw the conclusion that the length of the incubation period is a key factor to affect the spread of Ebola. We evaluate the model comprehensively, list its strength and weakness, and we find some directions to optimal our model.

Keywords **Ebola, SEIRS model, BP neutral network, Logistic grow**

Contents

1 Introduction

In 2014, the Ebola Virus Disease (EVD) which has disappeared for years reappeared. Worse still, the outbreak has been becoming more and more serious, especially in Guinea, Sierra Leone and Liberia. Although these countries have tried their best to control the epidemic, their sanitation system has been damaged and they are lack of adequate medical capabilities. As a result, a sense of fear spread among people, the tendency of the spread of the epidemic has never slowed down. Thus far, fighting against the Ebola has become a global consensus.

Suppose the World Medicine Association (WMA) has announced that their new medicine can stop the spread of Ebola and cure patients whose conditions are not that serious,and we need to design an efficient drug delivery system based on the medicine. Certainly, we deem that the medicine cannot cure people who are badly affected, or at most, they can only release their pain and improve their current condition. Besides, there are many factors which should be coordinated during the manufacturing and delivery process of the medicine. Therefore, in order to support countries suffering from Ebola, WMA needs to design a global plan to cope with Ebola.

To assist the association, we plan to design a strategy which must conform to the distribution of the epidemic and improve the current situation. Here are the factors that we will consider:

- The spread of Ebola
- The quantity of medicine that needed
- A possible feasible delivery system
- Destination of the delivery
- The speed of manufacturing the vaccine or drug
- Other factors we consider important and necessary

Our goal is to build an optimization model to eradicate the Ebola, or at least, reduce the severity of the current situation.

Through the interpretation of this problem, we deem that it belongs to the optimization

problem. We need to design an optimal plan based on the following factors, namely-- the spread of Ebola, the quantity of medicine that is needed, the designing of a delivery system, the selection of locations, the speed of vaccine and drug production and other factors related to Ebola eradicating. The feature of this problem is that we need to consider lots of factors. Therefore, several sub-models are needed to be built in order to analyze each factor respectively, and then, these sub-models should be integrated to evaluate the whole plan. The difficulty of this problem lies in the finding of the relations among those sub-models. For instance, the speed of manufacturing vaccine and drug can, to some extent, determine the designing of the delivery system. The selection of locations to be delivered to can be deemed as part of the whole designing of the delivery system. Besides, attention should be paid to some specific background information of this problem. For example, the Ebola mainly broke out in Sierra Leone, Guinea and Liberia. Therefore, our work will mainly focus on these three countries.

In the following paragraphs, we will list some literatures and works which will be related to our method. In 1927，Kermack and Mckendrick proposed a landmark method to research for infectious diseases: The Compartmental model. A specific theory—epidemic dynamics, has been well developed since then. The SIR model is the most classical one. It divides people into three parts: susceptible, infective and removal people. However, when considering some infectious diseases which include incubation period, the result of SIR model tends to be inexact. The SEIRS model is a kind of non-linear mathematic model which is used to describe people's dynamic behavior that can transform randomly among susceptible, exposed, infective and removed conditions. This model takes the exposed people, who are in the incubation condition into consideration. This factor is not included in the SIR model.

In the problem of medicine delivery, Albertod'Onofrio (*On pulse vaccination strategy in the SIR epidemic model with vertical transmission*, 2004) improved a result given by Lu et al. on the global asymptotic stability of the eradication solution of the PVS applied to diseases with vertical transmission. He also proved that the condition for local stability also guaranteed the global stability. Jiuh-BiingSheu (*An emergency logistics distribution*

approach for quick response to urgent relief demand in disasters, 2007) presented a hybrid fuzzy clustering optimization approach to the operation of emergency logistics co-distribution responding to the urgent relief demands in the crucial rescue period.Xu and Wang (*Dynamic vaccine distribution model based on epidemic diffusion rule and clustering approach*, 2010) introduced the SIQR model with pulse vaccination to describe the epidemic diffusion rule and obtain the demand of affected areas. Based on the SIQR model, the affected areas are clustered by using SOM neutral network to qualify the result.

From the literature review, we can conclude that the classical SIR model cannot match some characteristics of Ebola. So we select the SEIRS model which has the high similarity to Ebola. Besides, we still make some adjustments to it, for example, we have considered the high death rate of Ebola and people who have been cured are immune to the disease in a short time. That makes our result more reasonable. We obtain the value of the rate of effective contacts. We show some figures and tables to reflect the spread rule of Ebola. Finally, we obtain the quantity of medicine that is needed.

In the study of the **design of delivery system**, relative researches mainly focus on resource allocation in a short range or inside a country. What we need to deal with is a global problem of resource allocation among many countries. Therefore, many research achievements lose their meaning on this problem. We firstly describe the speed of manufacturing medicine refer to the classic Logistic growth model. By searching some information, we determine that producing countries include United States, Russia, China and Canada. When considering locations of delivery, we divide the most severe countries, Guinea, Liberia and Sierra Leone into smaller parts. Besides, surrounding countries like Mali, Senegal, Cote d'Ivorie and Nigeria are also in our consideration in preventing the diffusion of Ebola. In order to cut down the cost and make our work more practical, we set 10 days as a distribution period, and the whole plan can be adjusted timely according to the feedback. Therefore, the whole delivery system can be viewed as a discrete dynamic distribution process. We find the value of distance between these areas and producing countries. Finally, we transfer the problem into **a NLP problem** which belongs to optimal problems, and we find the local optimal solution.

Afterwards, we test our model and articulate the rationality of the model. Then we make slight modifications on certain parameters to analyze its sensitivity. Finally, we will analyze the strengths and weaknesses of our model and point out how to improve the model.

2 Assumptions and Justifications

To analyze the essence of the problem, we don't need to take every detail into our consideration. So we just simplify the problem by making following assumptions, each of which is properly justified.

- All susceptible individuals have the same probability to be infected.
- Fast-acting vaccine: According to an article published on the latest Nature, some American scientists have developed the fast-acting vaccine to deal with the deadly Ebola. Experiment show that it can be effective to prevent the infection of Ebola only 4 weeks after the injection. While previous reports say that it takes at least 6 months for vaccine to be effective.
- All inoculators are susceptible people. Since individuals in the incubation condition cannot show symptoms. In order to simplify the model, we make this assumption.
- There are no great natural disasters and other serious infectious diseases in affected areas during this time period.

Additional assumptions are made to simplify analysis for individual sections. These assumptions will be discussed at the appropriate locations.

3 Notations

All the constants and variables used in this paper are listed in **Table 1** and **Table 2**.

Table 1 Constant Symbols

Symbol	Definition	Value
u	The probability for exposed people turn to be cured people.	5%
α	The probability for exposed people turn to be infectious people.	95%
μ_E	The isolation rate of exposed people	0.0009
μ_I	The inoculation rate of the vaccine	0.001

Table 2 Variable Symbols

Symbol	Definition
$N(t)$	Total number of individuals
ω_1	The incubation period of the disease
ω_2	People who have been cured lose the immunity and become susceptible during this period
α	The ratio for individuals who transform from the incubation condition to the morbidity condition
β	The effective contact rate of individuals and the disease
γ	The ratio for patients that turned to be cured
b	The direct immunization rate for individuals
u	The ratio for individuals who transform from the incubation condition to the immunization condition.
c_{ij}	denotes the cost of a unit medicine that assumed during the delivery process in unit time
t_{ij}	denotes the delivery time from the country i to the affected area j
$p_{ij}(t)$	denotes the quantity of medicine delivered from the country i to the affected area j
$D_j(t)$	denotes the demand in the affected area j
$RP_j(t)$	denotes the actual quantity of medicine that is provided in the affected area j

$P_i(t)$	denotes the quantity of the medicine that country i can supply

4 Overview

The World Medicine Association (WMA) is a decision maker which can organize and coordinate the supply and distribution of medicine upon a disease. From **Figure 1**, we can see that when a disease like EVD breaks out, based on their assessments of affected areas, the WMA can design a practical plan to help the affected country eradicate the disease. When some medicine has been delivered to the affected area, the WMA can collect feedback information to update their assessment and modify their plan. Therefore, the WMA has the power to determine when and where the medicine should be supplied and distributed.

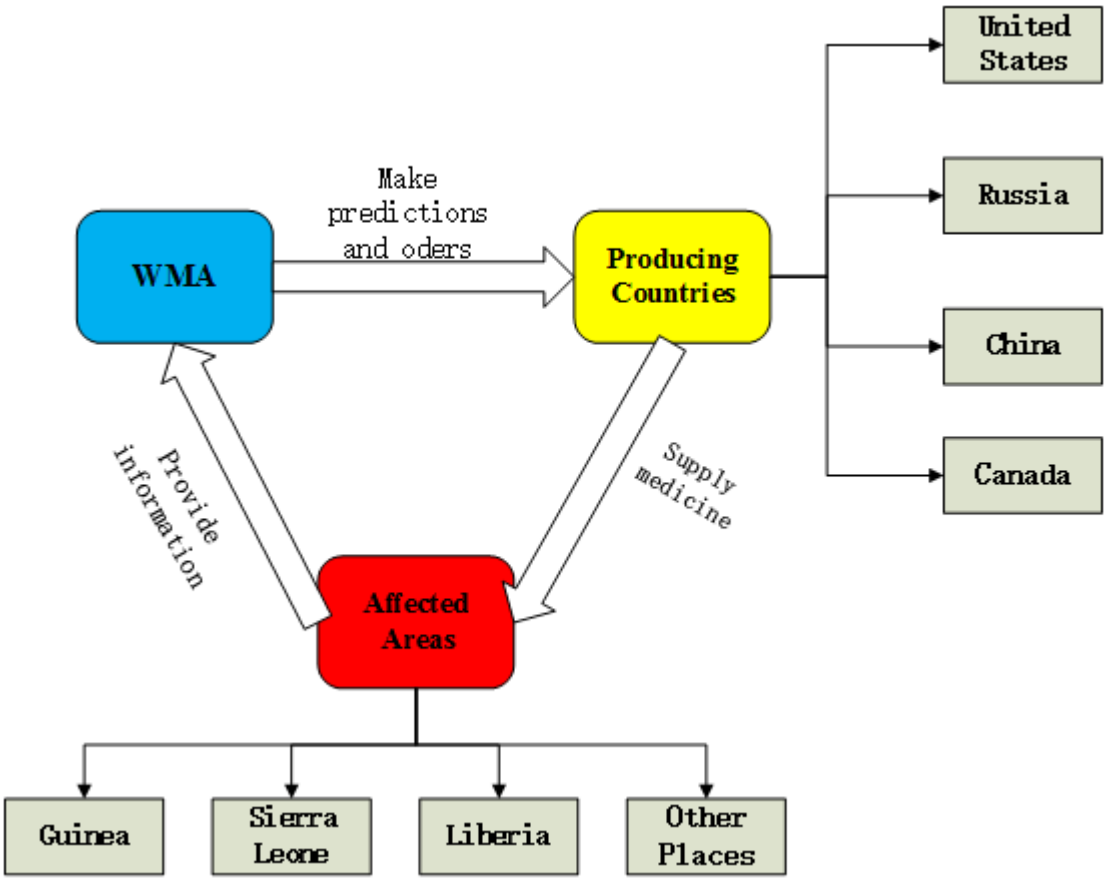

Figure 1 Overview of Our Model

5 The Model

5.1 Sub-Model i: Advanced S-E-I-R-S

5.1.1 Analysis of the Problem

5.1.1.1 A Review of Ebola

Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever, is a severe, often fatal illness in humans, with high infectivity and high mortality rate [1].

The length of incubation period is between 2 to 21 days, usually between 4 to 10 days. Recently, based on mathematical models, some people predict that around 5% of cases may take greater than 21 days to develop.

Patients of Ebola are infected with this disease mainly because of their contacts with body fluid or organs of animals who carry the virus. They may also catch the disease by touching appliances or tools with virus on. So far, evidence has not been adequate to demonstrate that the Ebola can spread among primates through air particles. Recovery may begin between 7 and 14 days after first symptoms. If death occurs, it will follow typically 6 to 16 days from first symptoms. For people who have been cured，they develop antibodies against Ebola that last at least 10 years, but it is unclear if they are immune to repeated infections. If someone recovers from Ebola, they can no longer transmit the disease. Our model conforms to these characters of the EVD. So the rationality of our model can be assured to a large extent [2].

5.1.1.2 S-E-I-R-S

Infectious disease is one kind of the most severe diseases to human health. During the research of the spread of infectious disease, the most meaningful work is the Compartmental model proposed by Kermack and Mckendrick in 1927[3]. This model is still in use nowadays, and a specific theory—epidemic dynamics, has been well developed. Epidemic dynamics use a non-linear dynamics method to build a mathematical model in order to research the spread of infectious disease. The model considers infectious disease in the view of not only pathological knowledge, but also the mechanism of transmission of

general infectious disease. It describes the spread process by quantity relation and analyze the change regulation of individuals. Thus, it can reveal the dynamic development of infectious diseases.

Among these models, the SEIRS model is a kind of non-linear mathematic model which used to describe people's dynamic behavior which can transform randomly among susceptible, exposed, infective and removed conditions. Since the SEIRS model has a good description on the change regulation of infectious disease among individuals. Based on the similarities and differences between the SEIRS model and characteristics of the Ebola (the death rate is not included), we improved the SEIRS model to fit our study on Ebola.

Table 3 The differences and similarities

	SEIRS	Ebola Virus
Differences	Virus has infectivity both in the incubation condition and the infected stage	Individuals have no infectivity during the incubation period, only patients have the infectivity.
	The death rate of the disease is neglected.	The Ebola virus has the high death rate which cannot be negligible.
	The cured individuals can become susceptible at a certain probability.	Cured people cannot be infected again in this model. Evidence can validate that the antibody can live for 10 years inside the human body.
	The natural mortality rate is included.	The birth rate of population counteracts the death rate.
Similarities	It has the saturated contact rate	There is no evidence to show that Ebola can spread through air. But we deem the speed of infectivity saturated if only the direct contact condition is considered.
	It has an incubation period	It has an incubation period.

5.1.2 Assumption of the Problem

We assume that there are two stages of the spread of the Ebola virus. The first one is that the medicine *has not been* manufactured and the second one is that the medicine *has been* manufactured.

We still **adopt some assumptions in the SEIRS** model.

- There is an equation:

$$S(t)+E(t)+I(t)+R(t)=1$$

Where

$S(t)$ denotes the ratio between the number of susceptible individuals and the total number of people in one country during the time period t .

$E(t)$ denotes the ratio between the number of individuals who are in the incubation condition and the total number of people in one country during the time period t , the disease has the infectivity at the same time.

$I(t)$ denotes the ratio between the number of individuals who are infected with the disease and the total number of people in one country during the time period t , individuals are more likely to be infected at the same time.

$R(t)$ denotes the ratio between the total number of individuals who have been cured and the total number of people in one country during the time period t .

- The initial condition is $(S(0),E(0),I(0),R(0))=(S^0,E^0,I^0,R^0)$, their values are all between 0 and 1. Parameters $u,b,\omega_1,\omega_2,\alpha,\beta,\gamma$ .in the model are all positive,where $0\le u,b,\alpha,\beta,\gamma\le 1,\omega_1\ge 1,\omega_2\ge 1$.
- We neglect the constant input rate of populations (including the birth rate， migration rate and emigration rate of individuals). Birth rate and death rate of population are not in our consideration neither.
- Infected individual cannot transform to patients to a certain proportion and are infectious until they go through the incubation period

Based on characteristics of Ebola, we conclude:

- There are 5 kinds of Ebola viruses. We assume the medicine can be effective in all 5 kinds' viruses.
- All recovered people, including people who have been cured and exposed people who have not transformed to patients, are immune to all 5 Ebola viruses during the time period we set in the model. Even if they have effective contacts with individuals who have been infected, they will not be infected again.
- Viruses in the body of infected individuals will firstly enter an incubation stage, and it will last for some time. This period is called the incubation period. Viruses in incubation stage will not cause morbidity. If these individuals contact with others effectively, they will not spread viruses to others.
- When the incubation stage of an individual ends, the individual will become a patient with a 90% probability. If individuals who are in morbidity condition contact with others effectively, the virus will be spread certainly.
- Patients can be cured to a certain probability.
- Susceptible individuals and individuals in incubation stage can obtain immunity by accepting vaccination. The immunity will last for some time.

5.1.3 Build the Model

Based on the above analysis, we build an advanced S-E-I-R-S as the following figure **Figure 2** shows.

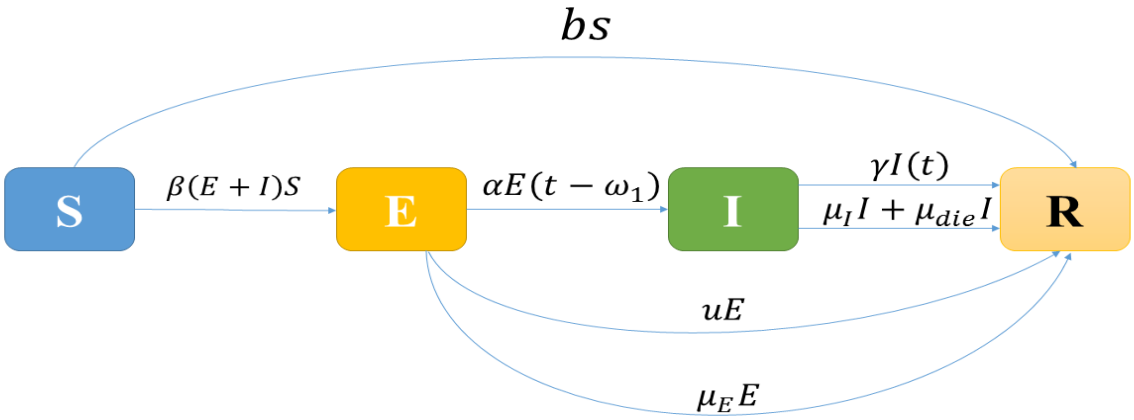

Figure 2 Advanced S-E-I-R-S

S-E-I-R-S:

$$N(t) = S(t) + E(t) + I(t) + R(t)$$

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -bS(t) - \beta(E(t) + I(t))S(t) + \gamma I(t - \omega_2)$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \beta(E(t) + I(t))S(t) - uE(t) - \alpha E(t - \omega_1)$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \alpha E(t - \omega_1) - \gamma I(t)$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I(t) + uE(t) + bS(t) - \gamma I(t - \omega_2)$$

Our model:

$$\frac{\mathrm{d}s}{\mathrm{d}t} = -bs - \beta(E + I)S$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \beta(E + I)S - uE - \alpha E(t - \omega_1) - \mu_E E$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \alpha E(t - \omega_1) - \gamma I(t) - \mu_I - \mu_{die}$$

$$\frac{\mathrm{dR}}{\mathrm{d}t} = \gamma I + uE + bs + \mu_I + \mu_E E$$

5.2 Sub-model ii: The Quantity of the Medicine Needed

5.2.1 Analysis of the problem

We take serious affected areas and places where epidemics are likely to breakout as our research objects. We consider that medicine needs to meet the requirement of two aspects: one is patients' demand for therapy medicine, another one is susceptible people's demand for vaccines.

The demand of medicine varies in terms to patients with different severities.

Susceptible patients can be divided into [4]:

- Health workers
- Family members or others in close contact with infected people.
- Mourners who have direct contact with the bodies of the deceased as part of burial ceremonies.

If the amount of medicine is restricted, we will distribute medicine to people whose disease are not serious enough and medical staffs in order to maximize the utilization of medicine.

Besides, considering the uncertainty and the validity of medicine. We believe that we should preserve enough medicine for emergencies.

5.2.2 Build the Model

We set locations which are the most serious and that next to them as demanders.

Since Guinea, Liberia and Sierra Leone have high severity of the disease. We divide these countries into smaller parts to restrain the spread of Ebola in a most efficient way.

Table 4 Different Locations

Locations that have high severity	Guinea (central part, southern part), Liberia (eastern part, western part, southern part, northern part) Sierra Leone (eastern part, western part, southern part, northern part)
Locations that have low severity	Nigeria, Mali, Senegal.
Locations that have high risk	Cote d'Ivorie

The demand of medicine is close to the number of infectious people. So we use the

model we have built in the first part to obtain the number of current infectious and susceptible people. Obviously, the spread speed of Ebola varies in different places. The effective contact rate is a key factor to evaluate the spread of Ebola. It is related to the density of local people, the number of educated people and the level of nation incomes.

We have obtained the value of the density of population, the rate of uneducated people, per-capita income and the effective contacts of Ebola virus. By using the **BP network**, we can predict the effective contacts of another 4 countries.

Table 5 World Statistics Annual

World Statistics Annual [5]								
Countries	The diffusion rate	The average income	The density of people	The illiteracy rate	Total in east/ patients	Total in west/ patients	Total in south/patients	Total in north/patients
Guinea	0.657	544.0	45.5	70%	400/1100	160/2000		
Sierra Leone	0.8101	483	79.4	70%	5000/95	5000/119	500/109	500/174
Liberia	0.6642	278	35.5	60.8%	1600/100	1600/100	500/100	5000/100
Nigeria	0.8955	1509	184.2	46.70%	17012/20			
Mali	0.5634	671	11.7	73.80%	145/8			
Senegal	0.6187	1132	65.3	47.9%	1286/1			
Cote d’Ivorie	0.6164	1196	66.7	48.7%	2330			

5.3 Sub-Model iii: Speed of Manufacture the Medicine

Now, let's talk about the speed of manufacturing the vaccine and drug.

On the early stage of the production, since the theory and technology are not mature, the speed will be comparatively slow. However, during the manufacturing process, the theory and technology is **becoming complete and mature**, the speed will be faster and faster.

But, **in the long run**, the speed is restricted by many factors, such as financial resources, lack of adequate raw materials and machines and so on. Thus, the speed cannot increase without any limits. We can infer that in the later stage of manufacturing, the speed will increase relatively slowly, and there will be **a supremum for it**.

We deem the speed of manufacturing medicine as a function of time. In order to simplify the model, we assume that this function can be differentiable. Since few of current literatures are suitable for this model, we plan to use classical **logistic growth model** to describe the function. Logistic growth model can well reflect the retardant growth. Although Logistic growth model tends to be used to study the growth of population, features shown in this model can match that in the Logistic growth model. Based on our considerations mentioned above, we assume that the speed of manufacturing medicine conforms to the logistic growth curve.

Here is the differential equation of logistics function:

$$\frac{dP}{dt} = r * P(1 - \mathrm{P}/\mathrm{K})$$

We could get its function expression easily:

$$\mathrm{P(t)} = \frac{K * P_0 * e^{r*t}}{K + P_0(\mathrm{e}^{r*t} - 1)}$$

And then, we can get such a function of speed：

$$v(\mathrm{t}) = \frac{v_{\max} * v_0 * e^{r*t}}{v_{\max} + v_0(\mathrm{e}^{r*t} - 1)}$$

Here are parameter descriptions:

- $v_{\max}$ denotes the **ideal maximal speed of manufacturing medicine** in a country.

We assume that the ideal maximal speed is the same for all countries, the value we set is 1000.

- t denotes time, the unit of which is one day.
- r is a parameter, which determines how fast the manufacturing speed approximates the supremum in one country. It becomes faster as r is getting larger.

5.4 Sub-Model iv: Delivery System

5.4.1 Analysis of the Delivery System

If there is enough manpower, we can deem that the manufacturing of medicine is a continuous process. Even if like this, we cannot deliver a medicine the moment it is produced, because it is not only meaningless, but also costly. From a realistic point of view, and in order to improve the condition in the affected area rapidly, planes can be used to deliver the medicine at a fixed time every 10 days. That is, the interval between two deliveries is 10 days, the amount of medicine in one delivery is what is produced in this interval. In that case, the whole delivery system can be deemed as a discrete dynamic distribution process. Since affected areas in the western Africa are different in time length after the disease outbreak and severity, the degree of emergency verifies. We need to make reasonable distributions according to the quantity of supply and demand. The distribution strategy will change every day. The WMA will predict the demand in each affected area after the delivery every ten days, so that they can manufacture and distribute medicine in a rational way.

On the early stage, the speed of manufacturing medicine is relatively slow and can hardly meet the demands, which means demands exceed supply. During this period, we need to take the severity of each affected area as an important factor. The strategy that we firstly distribute medicine to areas which are most severe should be followed. Therefore, in the early stage, under the condition that the structure of infected individual changes constantly, how to distribute finite resources reasonably and increase the efficiency

according to various severity is a key problem we need to solve. After this period, with the acceleration of manufacturing speed and decrease of patients, the demand will drop. The supply and demand of medicine will reach a balance, even, supply exceeds demand. To save resources, we control the quantity of medicine to be produced and let it equals what is needed.

5.4.2 Period A: Demand Exceeds Supply

During this period, since the supply cannot meet the demand, we set two objective functions:

To minimize the total transportation cost:

$$\min S = \sum_{\forall i} \sum_{\forall j} c_{ij} * t_{ij}$$

To minimize the shortage quantity of each delivery location[7]:

$$\min L_j(\mathrm{t}) = D_j(\mathrm{t}) - \sum_{\forall i} p_{ij}(\mathrm{t})$$

Subject to:

- $\mathrm{RP}_j(\mathrm{t}) = \sum_{\forall i} p_{ij}(\mathrm{t})$
- $P_i(\mathrm{t}) = \sum_{\forall \mathrm{j}} p_{ij}(\mathrm{t})$
- c_{ij} ,a function about $p_{ij}(\mathrm{t})$ .When $p_{ij}(\mathrm{t})=0$,that is, we won't have this flight.

  With the increase of $p_{ij}(\mathrm{t})$, c_{ij} also increase, we assume:

  $$c_{ij} = 10 * p_{ij}(\mathrm{t})$$

The medicine provided depends on the demand, the more it needs, the more we will provide.

5.4.3 Period B: Supply Exceeds Demand

During this period, since the supply exceeds the demand, we set one objective functions:

To minimize the total transportation cost:

$$\min S = \sum_{\forall i} \sum_{\forall j} c_{ij} * t_{ij}$$

Subject to:

- $\mathrm{RP}_j(t)=\sum_{\forall i} p_{ij}(t)$
- $P_i(t)=\sum_{\forall j} p_{ij}(t)$
- c_{ij} ,a function about $p_{ij}(t)$ .When $p_{ij}(t)=0$,that is, we won't have this flight.

  With the increase of $p_{ij}(t)$, c_{ij} also increase, we assume:

$$c_{ij}=10*p_{ij}(t)$$

6 Experiments

6.1 Advanced S-E-I-R-S

In order to obtain the value of parameters in differential equations, we adopt two methods:

Some parameters have on link with locations and kinds of infectious diseases. We set values which are commonly used in the infectious disease model for parameters.

Considering that effective contacts rate and recovery rate of virus are key factors which can affect the speed of spread of virus. Besides, these two factors are special due to characteristics of Ebola and locations, so common values are not suitable for them. So far, there has been no exact statistics about effective contacts rate and recovery rate. So we study on Guinea, Liberia and Sierra Leone. Data between 13th August, 2014 and 1st February, 2015 is regarded as the source of data. Based on the parameter fitting of differential equation set in the Simulink Design Optimization in MATLAB. Obviously, values of effective contacts rate and recovery rate are both between 0 and 1. According to experience and current infectious disease model, we set the value 0.3 and 0.02 for them respectively. The result is shown in **Figure 3 ~ Figure 8**:

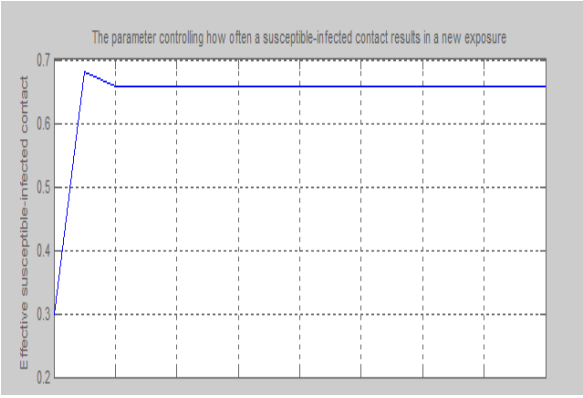

Figure 3 The parameter controlling how often a susceptible-infected contact results in a new exposure in Guinea

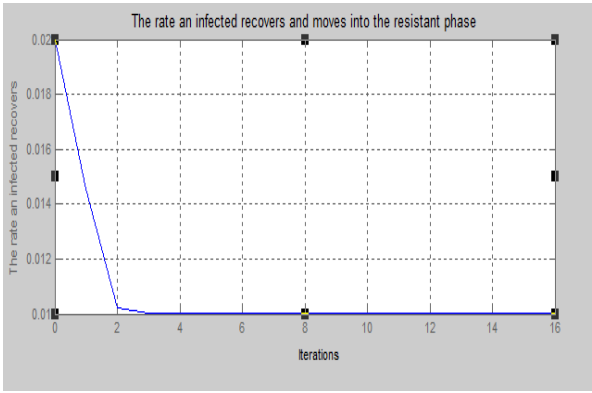

Figure 4 The rate an infected recovers and moves into the resistant phase in Guinea

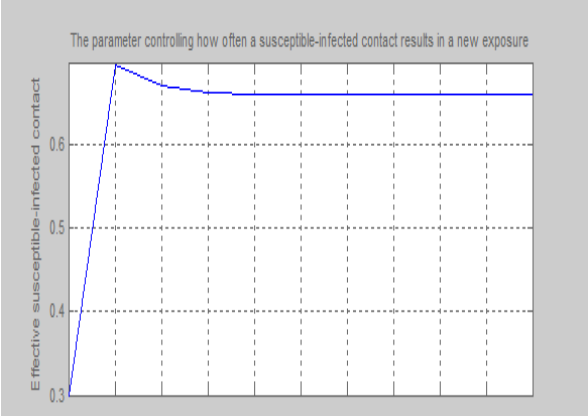

Figure 5 The parameter controlling how often a susceptible-infected contact results in a new exposure in Liberia

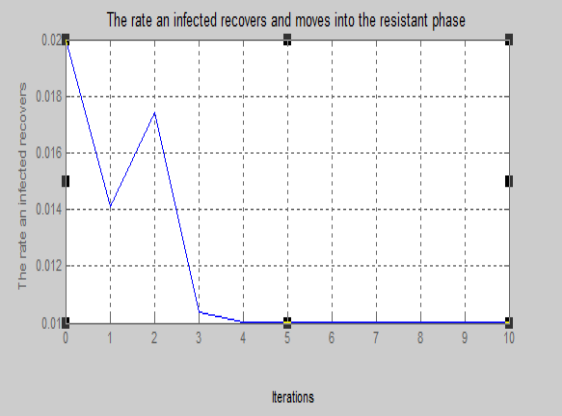

Figure 6 The rate an infected recovers and moves into the resistant phase in Liberia

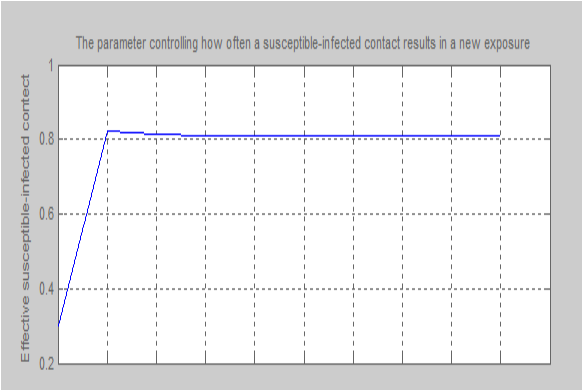

Figure 7 The parameter controlling how often a susceptible-infected contact results in a new exposure in Sierra Leone

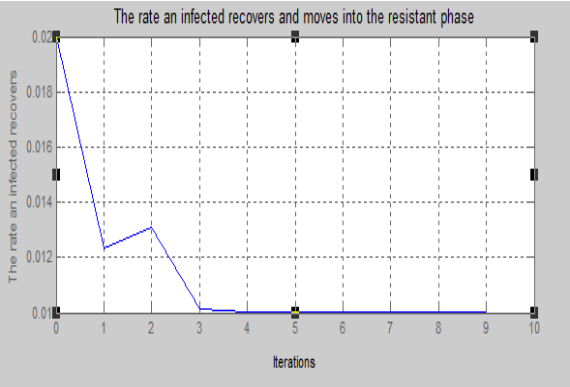

Figure 8 The rate an infected recovers and moves into the resistant phase in Sierra Leone

We surprisingly find that recovery rate for all three countries are the same (from **Table 6**), so it does, in fact. Before the vaccine is invented, no countries have obvious advantages in stopping Ebola, so the result is reasonable. Besides, the effective spread rate varies slightly among these three countries. It demonstrates that our model is comparatively rational.

Table 6 effective contacts rate and recovery rate of Guinea, Liberia and Sierra Leone

	Guinea	Liberia	Sierra Leone
effective contacts rate	0.6570	0.6642	0.8101
recovery rate	0.01	0.01	0.01

From **Figure 9**, we find the model matches the development trend of the disease in Guinea (We show the result in two figures since the order of magnitude of them varies a lot). In a general theory, the number of patients will reach a peak and drops to zero with the eradication of Ebola. But in the real world, the epidemic does not develop that quickly as the model illustrates. Because there many human factors during the development of the disease, parameters are different in different time period. With the increase of emphasis of the government and people's attention. The Ebola virus can be restrained to a large extent.

While in the classic SEIRS model, the number of patients increases rapidly and surpasses that of susceptible people. Obviously, that is not reasonable.

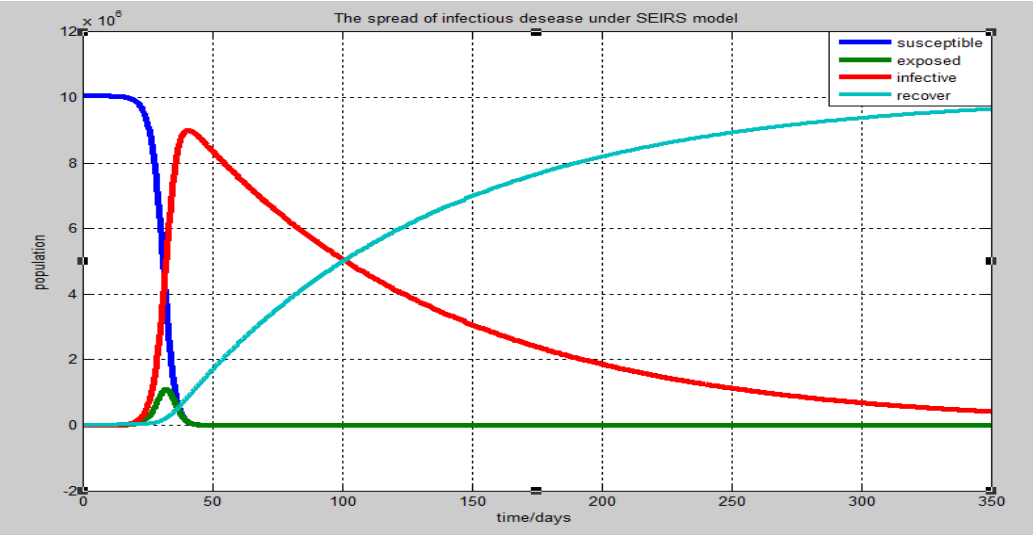

Figure 9 The spread of infectious disease under SEIRS model

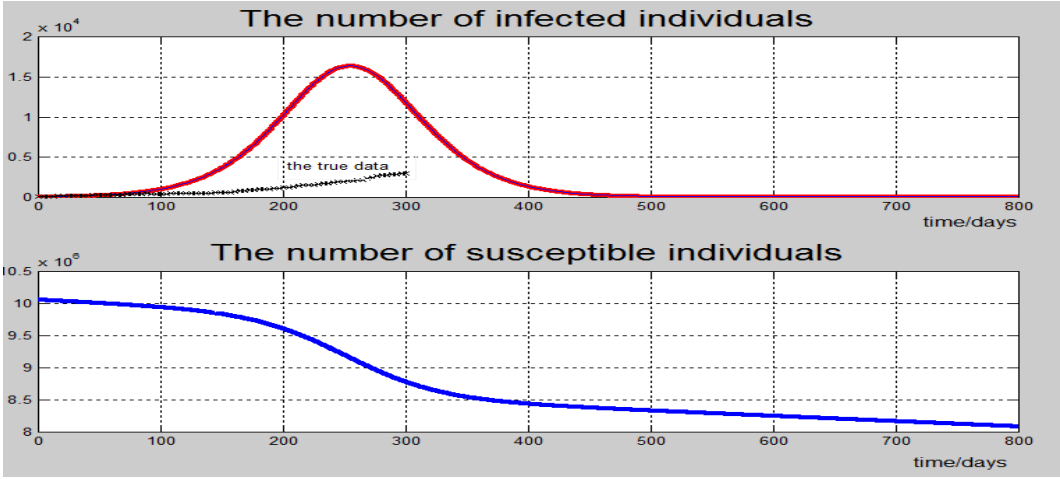

Figure 10 the spread of infectious disease under SEIRS

6.2 The Quantity of the Medicine Needed

Use the same model we calculate effective contacts rate in different countries:

Table 7 effective contacts rate in different countries

Guinea	0.657
Sierra Leone	0.8101
Liberia	0.6642
Nigeria	0.8955
Mali	0.5634
Senegal	0.6187
Cote d'Ivorie	0.6164

Use the calculation result in the differential equation of the first problem.

North Sierra Leone		Eastern Liberia(Western Liberia)		South Liberia		North Liberia		Nigeria	
infected individuals	susceptible individuals	infected individuals	susceptible individuals	infected individuals	susceptible individuals	infected individuals	susceptible individuals	infected individuals	susceptible individuals
500	1740000	1600	1000000	500	1000000	5000	1000000	0	170120000
2514	1656300	2852.2	945000	1190.3	952300	7768	923200	100	162870000
10685	1543700	5446.6	880500	2388.4	901200	12825	824800	700	155940000
31194	1346800	7858.7	806100	3873.5	845100	13787	720400	4000	149280000
46877	1064300	8240.2	730500	4949.3	785400	9683	636900	19200	142850000
31373	841600	6311.1	665800	4905.1	727200	4884	581400	76300	138460000
11869	731600	3708.3	616600	3809.9	676100	1966	544800	250100	129630000
3354	678400	1774.1	580000	2387.2	634100	673	517400	657500	121330000
806	644100	722.5	551000	1249.9	600000	202	494000	1294300	110400000
172	615500	256.9	526900	561.7	571100	54	472600	1731900	97380000
33	589000	80.8	503000	220.8	545500	13	452400	1499900	85380000
6	563900	22.6	481400	76.6	521800	3	433100	887400	76740000
1	539900	5.7	460900	23.6	499400	1	414700	399800	71110000
0	516900	1.3	441300	6.5	478100	0	397000	149100	67160000
0	494900	0.3	422500	1.6	457700	0	380100	48200	64000000

Figure 11 predicting infected individuals and susceptible individuals in different countries

North Sierra Leone		Eastern Liberia(Western Liberia)		South Liberia		North Liberia		Nigeria	
infected individuals	susceptible individuals	infected individuals	susceptible individuals	infected individuals	susceptible individuals	infected individuals	susceptible individuals	infected individuals	susceptible individuals
500	1740000	1600	1000000	500	1000000	5000	1000000	0	170120000
2514	1636300	2852.2	945000	1190.3	952300	7766	923200	100	162870000
10685	1543700	5446.6	880500	2388.4	901200	12825	824800	700	155940000
31194	1346800	7858.7	806100	3873.5	845100	13787	720400	4000	149280000
46877	1064300	8240.2	730500	4949.3	785400	9683	636900	19200	142850000
31373	841600	6311.1	665800	4905.1	727200	4884	581400	76300	136460000
11869	731600	3708.3	616600	3809.9	676100	1966	544800	250100	129630000
3354	678400	1774.1	580000	2387.2	634100	673	517400	657500	121330000
806	644100	722.5	551000	1249.9	600000	202	494000	1294300	110400000
172	615500	256.9	525900	561.7	571100	54	472600	1731900	97380000
33	589000	80.8	503000	220.8	545500	13	452400	1499900	85380000
6	563900	22.6	481400	76.6	521800	3	433100	887400	76740000
1	539900	5.7	460900	23.6	499400	1	414700	399600	71110000
0	516900	1.3	441300	6.5	478100	0	397000	149100	67160000
0	494900	0.3	422500	1.6	457700	0	380100	48200	64000000

Figure 12 predicting infected individuals and susceptible individuals in different countries

Mali		Senegal		科特迪瓦	
infected individuals	susceptible individuals	infected individuals	susceptible individuals	infected individuals	susceptible individuals
8	1450000	1	12860000	0.1	2330000
6.9587	1388200	1.2014	12312000	0.1186	2230800
8.0892	1329100	1.9321	11788000	0.1882	2135800
8.1337	1272400	2.668	11286000	0.2565	2044800
7.0979	1218200	3.172	10805000	0.3011	1957700
5.3858	1166300	3.2608	10345000	0.3058	1874400
3.5715	1116600	2.9051	9905000	0.2692	1794500
2.0751	1069000	2.253	9483000	0.2063	1718100
1.0602	1023500	1.5257	9079000	0.1381	1644900
0.4774	979900	0.9045	8692000	0.081	1574900
0.1902	938200	0.4713	8322000	0.0417	1507800
0.0672	898200	0.2164	7968000	0.019	1443600
0.0211	860000	0.0879	7628000	0.0076	1382100
0.0059	823300	0.0316	7303000	0.0027	1323300
0.0015	788300	0.0101	6992000	0.0009	1266900

Figure 13 predicting infected individuals and susceptible individuals in different countries

Since we assume that one medicine can be used for prevention, five for therapy. The inoculation rate of susceptible people is 0.004352. Therefore, we can calculate the amount of medicine in each location equals that used for treatment and for prevention.

6.3 Speed of Manufacture the Medicine

Since we have set the manufacture medicine model in section 4, at the same time, in order to test the model convenient, we give some necessary numerical illustrations. Also, we don't know v_0 and $v_{\max}$, so from the practical view, we make the following assumption:

- v_0=50
- $v_{\max}$=1000
- r determines how fast the manufacturing speed approximates the supremum in one country, based on medical level and nation power of producing countries (United States, Russia, China and Canada). We deem the order as:

$$r_{USA} > r_{\text{Russia}} > r_{\text{China}} > r_{\text{Canada}}$$

We set values of 0.05, 0.06, 0.07 and 0.08 for them respectively. The function is shown as follows.

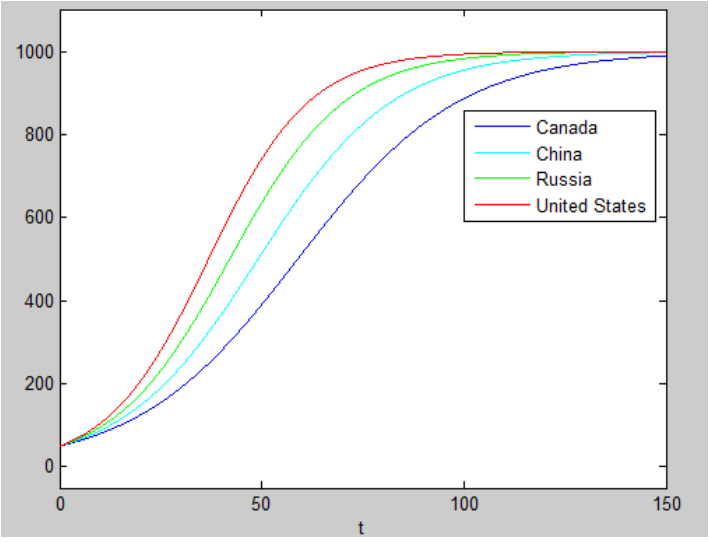

Figure 14 Speed of Manufacture the Medicine of Different Countries

6.4 Delivery System

Since we can determine the dynamic distribution according to different predictions,

delivery methods are not the same for every place. Our delivery methods can be divided into two phases. Considering the comprehensiveness of testing a model as long as avoiding troubles, we test these two phases respectively.

First of all, our producing countries include United States, China, Canada and Russia. Secondly, according to the severity in Guinea, Liberia and Sierra Leone, we divide the whole affected areas into the following parts: central Guinea, southern Guinea, western Sierra Leone, eastern Sierra Leone, southern Sierra Leone, northern Sierra Leone, western Liberia, eastern Liberia, southern Liberia and northern Liberia. We also consider countries which are surrounding these three countries. Though there are few non-infected people, we can prevent the further development of Ebola by doing so.

The following figure shows time for a plane to fly from producers and demanders [8].

Table 8 Time(h) for a plane to fly from producers and demanders

	United States	**Russia**	**China**	**Canada**
Central Guinea	19	14	16	23
Southern Guinea	18	13	15	22
Western Sierra Leone	20.5	23.5	15.5	23
Eastern Sierra Leone	18	21	13	21
Southern Sierra Leone	19	22.5	14	22
Northern Sierra Leone	19	22.5	14	22
Western Liberia	35	14	15.5	19
Eastern Liberia	33	12	14	17
Southern Liberia	34	13	14	18
Northern Liberia	34	13	14	18
Nigeria	14	12	14	17
Mali	20	11	14.5	21.5
Senegal	7	11	15	18
Cote d'Ivorie	19.5	15	23	20

6.4.1 Demand Exceeds Supply

In the early stage, we deliver and distribute the first batch of medicine. We should integrate the producing speed and obtain the amount:

$$N_{medicine} = \int_0^{10} \frac{v_{\max} * v_0 * e^{r*t}}{v_{\max} + v_0(e^{r*t} - 1)} dt$$

We put the value of r of each country in the formula above respectively. And we neglect the decimal part.

Table 9 The medicine each country can produce in the early stage

Country	United States	Russia	China	Canada
Dose	743	706	671	638

In this phase, since demand exceeds supply, we will first distribute medicine to infected people. If medicine remains, we will distribute them to susceptible people.

Table 10 The distribution in the early stage

	United States	Russia	China	Canada
Central Guinea	50	47	45	42
Southern Guinea	50	47	45	42
Western Sierra Leone	79	76	73	71
Eastern Sierra Leone	79	76	73	71
Southern Sierra Leone	50	47	45	42
Northern Sierra Leone	50	47	45	42
Western Liberia	50	47	45	42
Eastern Liberia	50	47	45	42
Southern Liberia	50	47	45	42
Northern Liberia	79	76	73	71
Nigeria	50	47	45	42
Mali	50	47	45	42
Senegal	50	47	45	42
Cote d'Ivorie	6	8	2	5

6.4.2 Supply Exceeds Demand

In this phase, we choose the fifteenth batch of medicine to deliver and distribute. We can easily verify that during the delivery, supply exceeds demand. We should integrate the producing speed and obtain the amount:

$$N_{medicine} = \int_{140}^{150} \frac{v_{\max} * v_0 * e^{r*t}}{v_{\max} + v_0(e^{r*t} - 1)} dt$$

We put the value of r of each country in the formula above respectively. And we neglect the decimal part.

Table 11 The medicine each country can produce in later period

Country	United States	Russia	China	Canada
Dose	9992	9972	9962	9947

Since supply exceeds demand, we distribute medicine to the locations that needs.

Table 12 The distribution in the early stage

	United States	Russia	China	Canada
Central Guinea	2366	2366	2366	2366
Southern Guinea	946	946	946	946
Western Sierra Leone	238	238	238	238
Eastern Sierra Leone	244	244	244	244
Southern Sierra Leone	326	326	326	326
Northern Sierra Leone	539	539	539	539
Western Liberia	460	460	460	460
Eastern Liberia	460	460	460	460
Southern Liberia	498	498	498	498
Northern Liberia	100	80	70	55
Nigeria	817	817	817	817
Mali	858	858	858	858
Senegal	761	761	761	761
Cote d'Ivorie	1379	1379	1379	1379

7 Sensitivity

The general character of infectious diseases is that they all have incubation period. The period of Ebola lasts for 21 days, so we change the length of the incubation period to show how it can affect the spread of Ebola.

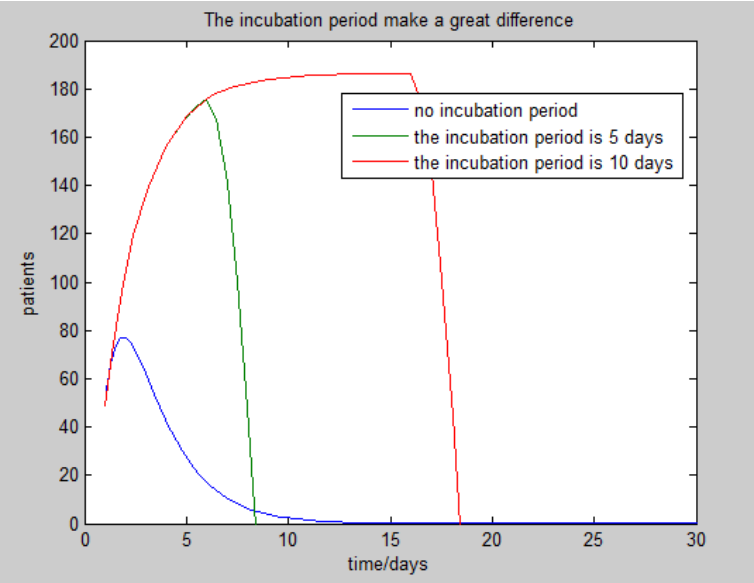

Figure 15 How the length of incubation affects the spread of Ebola

From **Figure 15**, we can find that three curves overlap in the early stage, so the length of the incubation period does not change the speed of spread of Ebola, but it changes the eradicating time (the point of intersection of the curve and the time axis means the total eradication of Ebola). Afterwards, however, with the increase of the length of the incubation period, the date of eradication progresses by several days. Since the length of the incubation period of Ebola virus is around 21 days, which is larger than 10 days set there, we can explain the reason why Ebola is hard to be eradicated from the view of the incubation period.

8 Strengths and Weaknesses

8.1 Strengths

- We take plenty of factors into our consideration, so we make lots of improvement of the classical SIR model to let it suitable for realistic conditions.
- We creatively adopt the Logistic growth model to estimate the speed of manufacturing medicine. Since we have considered the whole process of producing medicine, the result is quite reasonable and meaningful.
- We have considered the relationship between demand and supply: supply exceeds supply and supply exceeds demand. Thus, the model is more reasonable.
- We take into full account differences in various modes of transportation. We adopt the discrete dynamic distribution method which can cut down the cost significantly.
- Our models are connected with each other organically, as the figure we have shown in the ‘overview’ section. As a result, our model is strong because of its discrete setup.
- Our model can achieve the initial goal effectively. Flexibly, it can deal with a large quantity of data and statistics.

8.2 Weaknesses

- Since some specific data have not been found yet, we have to make some proper assumptions before building the model. If there are enough data and statistics, we will obtain a better result.
- We have not given a reasonable explanation for the second sub-model theoretically.
- Indeed, there is a fundamental tradeoff here between realism and elegance, and our model arguably veers toward over realism.

9 Conclusion

Nowadays, international disaster relief has not attracted extensive attention, especially on medicine of infectious disease. We need to consider some important issues and raise publics' attention by addressing this paper.

Suppose the World Medicine Association (WMA) has announced that their new medicine can stop the spread of Ebola and cure patients whose conditions are not that serious , we study on the spread rule of Ebola. We analyze and predict the condition in the affected areas and design a complete delivery system. At last, we provide a practical plan to deliver medicine.

First of all, we improved the SEIRS model by combing features that Ebola has high death rate and can spread fast. Through the sensitivity analysis, we find that the long incubation period let Ebola hard to be eradicated.

Secondly, considering differences in economy, medical level and education among locations, the spread will be various. We focus on serious affected areas and places which have high potential to break out diseases. We estimate the effective contacts rate through BP neutral network. We set sequences for medicine distribution according to the number of potential patients and susceptible people. Thus, the quantity of vaccine and drug can be determined.

Finally, we take the producing countries into our consideration. We creatively use the Logistic growth model to simulate the manufacturing speed. The whole delivery process is divided into two phases. When the supply of medicine is restricted, we make the distribution plan according to the priority. Thus the utilization of medicine can be maximized.

10 Future Work

Our model is a discrete model which only can reflect the trend of the development of the disease. It lacks the meaning in quantity. However, if we can set a certain parameter as a function of time, this model can be transformed to a continuous model. Thus, it can be more suitable for the actual condition in affected areas and has the function to predict precisely.

In the model of the manufacturing speed, we creatively adopt the Logistic growth model to describe the relationship between the speed and time. However, if we can insight into the specific process during the production of the medicine, we will obtain the quantitative relationship between the speed and certain factors. Thus, we can make some modifications to optimize our result.

In the model of the delivery system, based on the realistic thinking, it is a delivery process among nations. The whole process can be cut into two steps: firstly, the medicine has to be delivered to locations mentioned above, and then they can be distributed to sub-locations (small cities or towns). We mainly discuss the first step and nearly neglect the second step. Given more time, we plan to build another model so that the distribution can be discussed in detail. We believe that it’s easy to build the model since there are many researches focus on a distribution plan inside a country.

Besides, during the process of delivery, we should consider not only the transportation of vaccine and drug, but also some goods like food and water. Thus, we can assist the affected areas to fight against Ebola in all directions.

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A Dynamic Drug Delivery System Based on the Ebola Outbreak

（中文提纲）

基于埃博拉疫情的动态药物运输系统

一、 摘要

当前，对埃博拉疫情的控制已经成了全球范围内的一个热点话题。本文中，我们综合考虑了药物生产速度，药物发放地，以及药物需求量等因素，建立了一系列关于埃博拉疫情的传播和抗疫情药物传输系统的模型。

二、 研究现状

首先，目前大多数对疫情的研究都是基于简单的模型，但由于埃博拉疫情的特殊，这些模型对于埃博拉疫情来说，都并不是那么适合。其次，当前大多数研究者很少考虑药物生产速度这样一个关键因素，基本都视其为一个常数或正比例函数，这使得他们的结果并不是特别有信服力。最后，对于运输系统的设计来说，大多数研究者主要关注于如何在一个小的区域内或者一个国家内进行分配，很少有人研究如何多国合作进行药物运输系统的设计。

三、 提出模型

1. 出发点

首先，基于以往研究的不足，对于疫情传播模型，我们打算建立一个基于埃博拉疫情特点的改进的 S-E-I-R-S 模型，以便更加合理地预测埃博拉疫情变化的趋势。其次，对于药物生产速度模型，我们综合考虑了人们对药物的研究以及生产材料的限制，打算建立了一个 Logistic 模型，以便更加合理地描述药物在整个疫情控制中的发展状况。再者，对于药物运输系统的设计，我们考虑到药物生产速度的不同，决定将整个运输过程分为两个大过程：供不应求与供过于求。针对于每个阶段，采用不同的策略进行运输。最后，对于整个过程来说，仍然是一个动态的过程，药物的运输会根据地区疫情的不同而进行相应的分配。

2. 模型概览

国际药物联合会（WMA）是一个决策者，它能够在发生疫情时组织和协调药物的供应以及分配。从中可以看出，当疫情爆发时，他们可以对受影响地区进行评估，来设计一个可行的方案来帮助受影响的国家消除疫情。当一些药物被运送到疫区时，WMA 可以收集反馈信息来更新他们的评估，从而对原方案做出调整。因此，WMA 有权利去决定什么时候，在什么地区，药物可以被供应与分配。

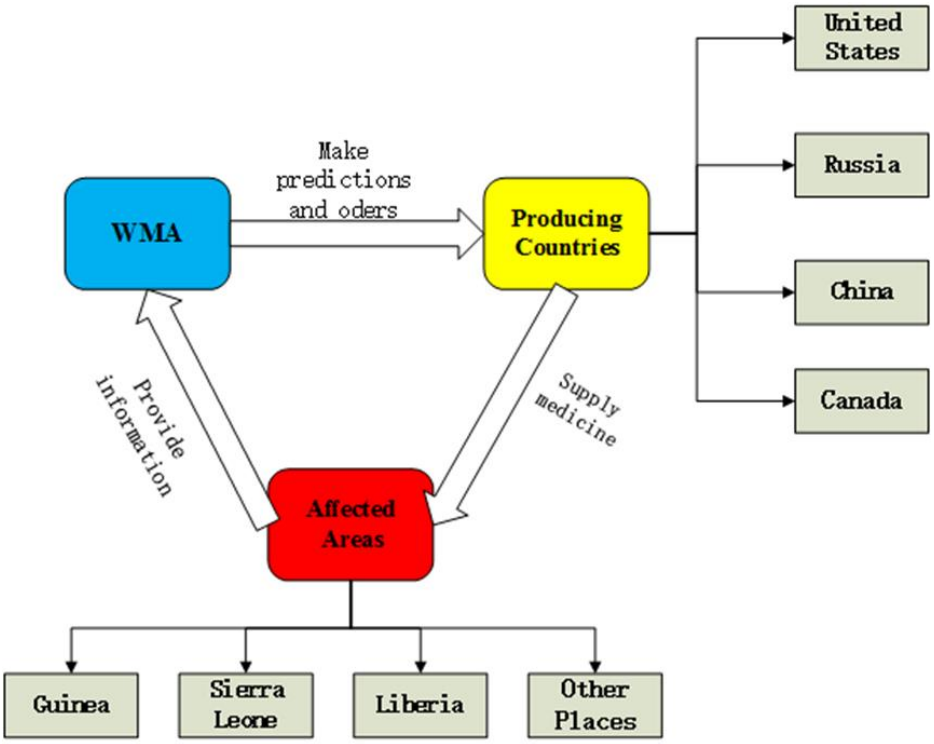

图 1 模型框架图

3. 模型简述

i. 改进的 S-E-I-R-S 模型

我们基于经典的 S-E-I-R-S 模型，创造性地建立了一个更加适合于埃博拉疫情的模型，如图 2

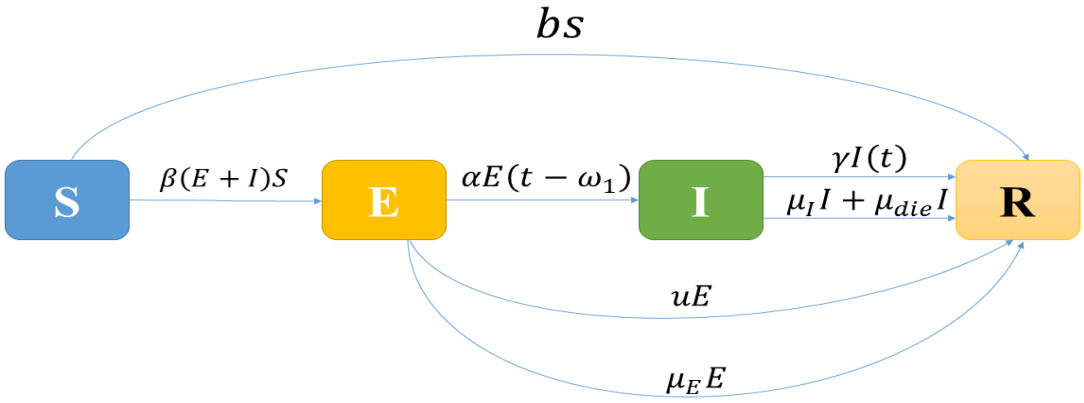

图 2 改进的 S-E-I-R-S 模型

在模型的建立过程中，我们考虑了八项影响因素，同时借助于 Simulink Design Optimization of MATLAB，将参数设置到不同模型的方程组中。正如通过分析我们得出，有效接触率是预测埃博拉传播速度的一个关键因素。

ii. 药物需求量模型

根据疫情爆发以来的数据，选取人口密度、医疗水平、经济区位三个因素作为有效接触率的主要影响因子，基于 BP 神经网络，我们对受感染的国家的有效接触率进行了预测。

为了简化药物需求模型，我们合理地将用于预防和治疗的药物需求量之比定为 1：10，基于这些基本假设，对药品需求量进行了预测(由于数据过多，请参见英文论文)。

iii. 生产药物速度模型

我们创造性地采用了经典的 logistic 增长模型，并分析了其在理论上的合理性。然后，我们绘制出了抗疫情药物在四个生产国的生产速度预测图，如图 3 所示

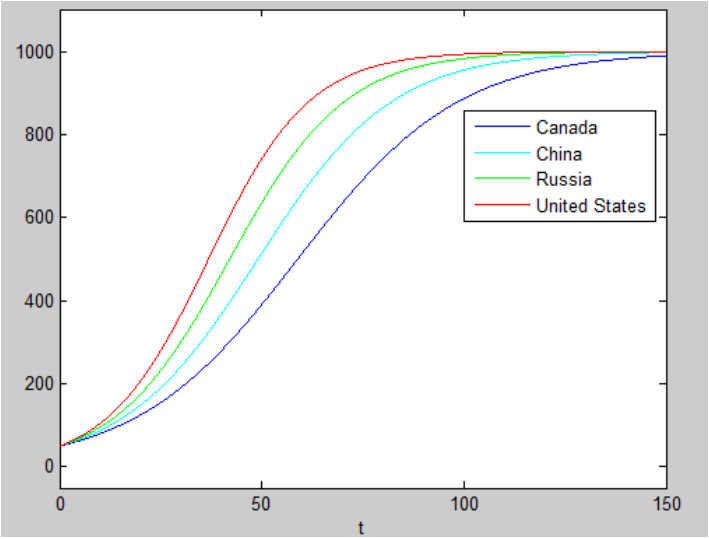

图 3 药物生产速度模型

iv. 运输系统模型

我们将整个过程分成两个阶段：供不应求和供过于求。并且根据不同的情况设置了不同的运输策略。我们将整个受疫情影响的地区细化成 14 个区域，以 10 天为一个运输段，将整个疫情防控过程看作是一个离散的动态过程。通过加入一些限制条件，我们将其转化成一个 NLP 问题，即最优化问题，进一步得到了局部最优解。这里我们给出两个阶段中某一个运输段的数据。

表 1 供不应求阶段药物的分配

	United States	Russia	China	Canada
Central Guinea	2366	2366	2366	2366
Southern Guinea	946	946	946	946
Western Sierra Leone	238	238	238	238
Eastern Sierra Leone	244	244	244	244
Southern Sierra Leone	326	326	326	326
Northern Sierra Leone	539	539	539	539
Western Liberia	460	460	460	460
Eastern Liberia	460	460	460	460
Southern Liberia	498	498	498	498
Northern Liberia	100	80	70	55

Nigeria	817	817	817	817
Mali	858	858	858	858
Senegal	761	761	761	761
Cote d'Ivorie	1379	1379	1379	1379

表 2 供过于求阶段药物的分配

	United States	**Russia**	**China**	**Canada**
Central Guinea	2366	2366	2366	2366
Southern Guinea	946	946	946	946
Western Sierra Leone	238	238	238	238
Eastern Sierra Leone	244	244	244	244
Southern Sierra Leone	326	326	326	326
Northern Sierra Leone	539	539	539	539
Western Liberia	460	460	460	460
Eastern Liberia	460	460	460	460
Southern Liberia	498	498	498	498
Northern Liberia	100	80	70	55
Nigeria	817	817	817	817
Mali	858	858	858	858
Senegal	761	761	761	761
Cote d'Ivorie	1379	1379	1379	1379

四、 灵敏度分析

我们最后对模型进行灵敏性分析，我们试着对埃博拉的潜伏期的长短进行实验，以便于知道它对埃博拉疫情的传播影响大小。正如图 4 所示，结论是疫情的潜伏期是影响埃博拉传播的一个关键因素。

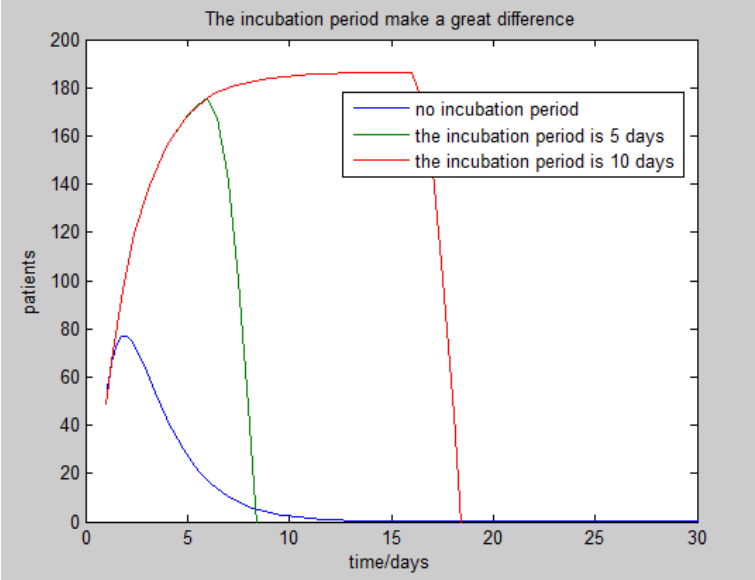

图 4 潜伏期对疫情传播的影响

五、 综合评价

相对于过去的关于疫情控制的模型，我们具有如下的优点：

1) 我们创造性地采用了 logistic 增长模型来评估药物生产速度模型，这是以往模型中所没有的。而且由于我们仔细考虑了整个药物生产过程，我们所得到的结果很有意义。

2) 我们仔细考虑了药物需求量与药物生产量之间的关系，将整个药物运输模型划分为了两个阶段：供不应求与供过于求。这使得我们得到的结果更加合理化。

3) 对于整个模型来说，我们基于 WMA 对每个地区疫情的评估，建立了一个离散动态的运输系统，这使得我们的模型适应性更强。

当然，我们的模型也有不足：

1) 我们所做的模型，仍然基于了一些比较强的假设。如果我们可以将这些假设弱化一点，我们的模型应该会更加具有实用性。

2) 在第二个子模型中，我们借鉴了 BP 神经网络的预测功能，并没有在理论上给出它的合理解释。