Team Control Number

38403

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2019 Mathematical Contest in Modeling (MCM) Summary Sheet

(Attach a copy of this page to your solution paper.)

Abstract

A new medication may prevent the spread of Ebola virus and cure those patients in the early affected period. How to make full use of the new medication to fight Ebola is of great concern and top priority. We are going to establish two mathematical models: one to predict the infection trend of Ebola virus, the right quarantine time and appropriate dosage; the other to explore the optimal distribution in transportation systems and production rate.

Model One will center on Ebola virus infection trends, quarantine time and the amount of medication. According to the characteristics of Ebola virus transmission, An Ordinary Differential Equation (ODE) model of virus transmission is built, along with the relevant graphics. On the basis of phase trajectories, discussions are made about the nature of ODE model of the spread of disease, the entire process of virus transmission and the best time for initial virus isolation is calculated. A nonlinear regression analysis is performed to test the reliability of the model.

Model Two will explore the optimal medication distribution within transport systems and the optimal drug production rate. Some specific mathematical models are created by linear programming in order to save the transportation time.

The Mathematical Model of the Optimized Use of Ebola Virus Drug

Team # 38403

August 9, 2019

1 Introduction

1.1 The basic situation of Ebola virus

Ebola is a cause in humans and other primate and mammals, with a high mortality rate of 50% to 90% [1]. It is of great importance to develop an effective medicine. World Medication Association declared that the newly develop drugs can cure the less seriously affected patients. Therefore the key of our model is to help with the effective use of the life-saving drugs.

1.2 The Direction of Research

The main direction of our research is to use a variety of mathematical methods and means to achieve the optimal use of the drug and the full value of drug, thereby reducing the Ebola virus infection rate and mortality.

2 Problem Analysis

2.1 The Restatement of the Problem

Ebola virus appeared resulted in the death of many patients, the Medical Association developed a drug to cure patients yet to come late, so that more patients get second chance to see the hope of life.

The model we build contributes to the crucial role the medicines play at the moment.

Factors that play a crucial role in the influence of drugs, including the speed of the disease, isolation time, the amount of drug required drug, delivery systems and drug production speed. Thus our tasks are gradually clear.

The task is as follows:

- The establishment of the Model One is to be more intuitive to see the trends in the spread of Ebola virus.The model not only provides important information for Ebola virus' prevention and treatment but also a similar model for the spread of other virus.

- Using the conclusion of Model One, we can calculate the isolation time roughly and then calculated the drug dosage further.
- Searching the database of the infected cases and using the nonlinear regression “nlinfit” analysis to test the reliability of Model One.
- The establishment of the Model Two is to explore the best transportation system for drug distribution, so that we can save drug delivery time and strive to save more patients.
- Using the Model Two elaborating the drug delivery rate and drug production speed is to calculate vaccines and drugs production speed.
- Using the speed of medicine transport and production in Model Two to further calculate the rate of vaccine and medicine production.

2.2 The Layout of Problem Solving

- First of all, we need to establish the ordinary differential equation models of the spread of Ebola virus(Model One), draw images, describe propagation of Ebola virus and discuss the characteristics concerned the solution. At the same time, using of the model we can calculate the best time to isolate rough.
- Secondly, use the results of Model One to identify positive relationship between dosage and the number of infections including time parameter variables, and then we can calculate the total dose.
- Thirdly, according to the database provided by World Health Organization(WHO), drawing scatter plots and using the nonlinear regression “nlinfit” analysis to test the reliability [6].
- Fourthly, using linear programming model in the use of transport,we establish transport system of Ebola drug.
- Fifthly, using the results of optimal transport from Model Two to determine the nonlinear relationship between production rate and optimal distribution and calculate the vaccine and medicine production rate.

- Finally, according to the results of our research, write a non-professional letter for the World Medical Association's announcement.

3 Model Design

3.1 The Spread of the Ebola Virus

For convenience, we define some symbols:

$i(t)$	total cases on t-th day.
$i(0) = i_0$	total cases on beginning.
N	population in this area.
k	infect factor
$r(t)$	number of people exited from the epidemic process on t-th day.

Modeling:
Case 1:
Assumptions:

1. There is no body recovered or died in the present period.
2. Population N remains, it means that we don't care population death, birth and flow.
3. Take k_0 as the number of people infected by a patient in one day.

The increasement of cases from t to $t + \Delta t$ is:

$$i(t + \Delta t) - i(t) = k_0 i(t) \Delta t \tag{1}$$

we can get a ordinary differential equations model for equation (1):

$$\begin{cases} \frac{\mathrm{d}i(t)}{\mathrm{d}t} = k_0 i(t) \\ i(0) = i_0 \end{cases} \tag{2}$$

the solution of equation (2) is:

$$i(t) = i_0 e^{k_0 t} \tag{3}$$

the figure of equation (3) is Figure 1:

Figure 1 shows us that the Ebola virus spread increases exponentially. The results confirmed to the fact that Ebola spreads very

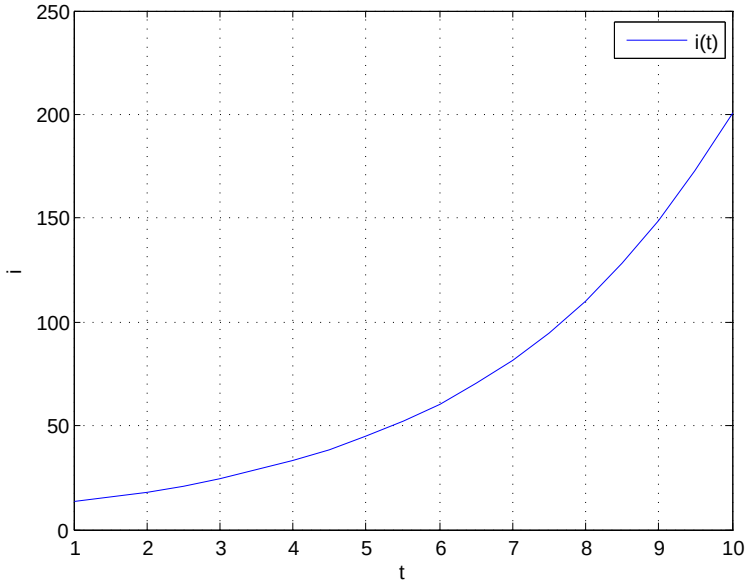


Figure 1: Spread of Ebola virus.

rapidly in the initial stage and the infected cases increase in the exponential function: when t tends to infinity, then $i(t)$ tends to infinity. But in the late situation of the Ebola virus is not fit, because in the patients's effective contact crowd, have healthy people and patients, while only health personnel can be infected. And part of patients will die in this period.

Improve this model, then we have case 2.

Case 2:

Assumptions:

1. Assuming infected and cured with long-term immunity, does not consider the case of long-term repeated infections, healthy immediately after infection can become infected persons. In this case, the people of the entire region is divided into three categories: The first category is contagium which able to infect others, indicating the number of such moment t with $i(t)$; second category is susceptible which vulnerable to becoming infected, with $s(t)$ represents the number of such moment t; the third category is a person other than the two categories above, including death after infection, get a long-term immunity after illness, who are no longer infected, represents the number of such moments t with $r(t)$.

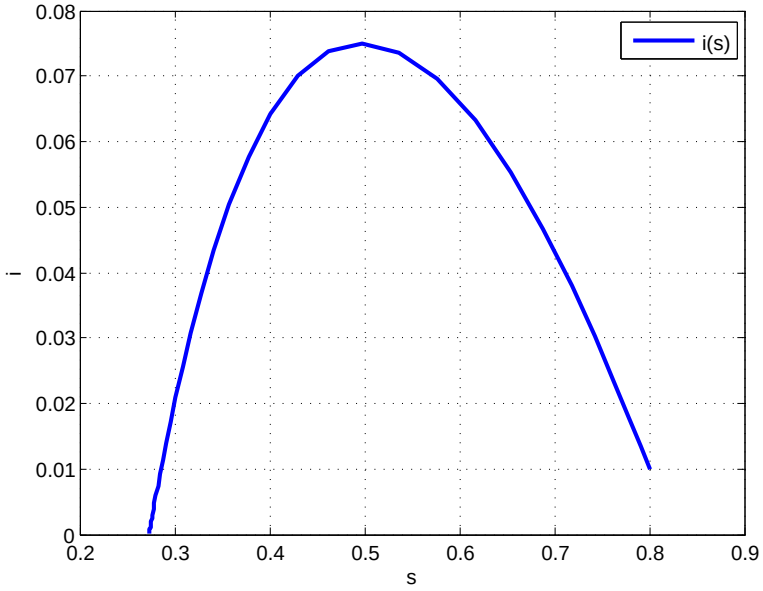


Figure 2: Phase trajectoriesthe for equation (7)

2. The region's total population N remains during the discussion, that is not considered births, deaths, flow and so on.

3. The speed of change from first class to second class is proportional to the number of first class.

$$k = \frac{k_0}{s(t)} \tag{4}$$

$$l = \frac{\frac{\mathrm{d}r(t)}{\mathrm{d}t}}{i(t)} \tag{5}$$

$$\begin{cases} \frac{\mathrm{d}r(t)}{\mathrm{d}t} = li(t) \\ \frac{\mathrm{d}i(t)}{\mathrm{d}t} = ks(t)i(t) - \frac{\mathrm{d}r(t)}{\mathrm{d}t} \\ \frac{\mathrm{d}s}{\mathrm{d}t} = -\frac{\mathrm{d}i(t)}{\mathrm{d}t} - \frac{\mathrm{d}r(t)}{\mathrm{d}t} \end{cases} \tag{6}$$

where $i(0) = i_0, s(0) = s_0, r(0) = r_0 = N - i_0 - s_0$.

$$\begin{cases} \frac{\mathrm{d}i(t)}{\mathrm{d}t} = ks(t)i(t) - li(t) \\ \frac{\mathrm{d}s(t)}{\mathrm{d}t} = -ks(t)i(t) \\ \frac{\mathrm{d}r(t)}{\mathrm{d}t} = li(t) \\ i(0) = i_0, s(0) = s_0, r(0) = r_0 = N - i_0 - s_0 \end{cases} \tag{7}$$

Equation (7) is difficult to obtain an accurate solution, can be the

first to make numerical calculations.

Numerical calculation: For convenience of calculation, visual $s(t)$ and $i(t)$ is the proportion of the total number, and therefore, in equation (7), set $k = 1$, $l = 0.5$, $i(0) = 0.01$, $s(0) = 0.80$, using MATLAB software programming as Appendix 1 and 2, product Figure 2 for $i(s)$.On the phase plane $s - i$, the domain of the phase trajectories is $D = \{(s,i), s > 0, i \geq 0, s + i \leq 1\}$.
Elimination t, then:

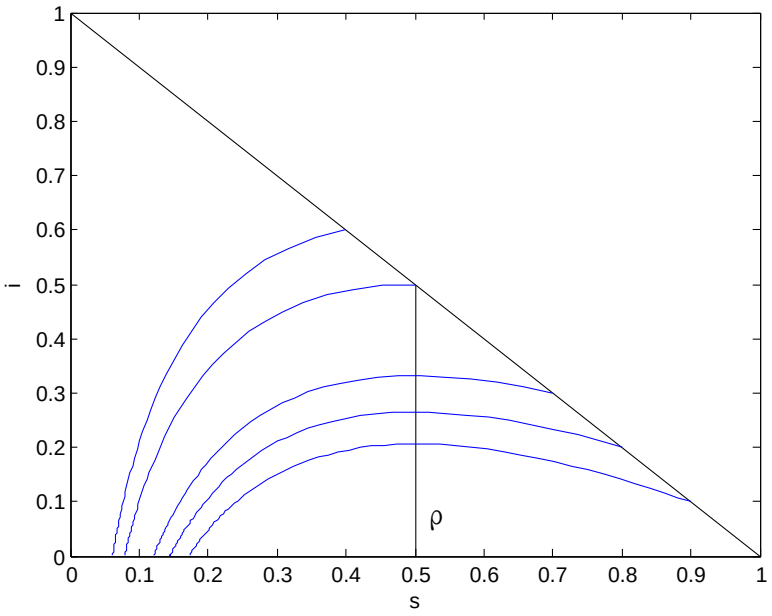
$$\frac{\mathrm{d}i}{\mathrm{d}s} = -1 + \frac{1}{ks} \tag{8}$$

Set $\rho = l/k$, said ρ is a characteristic (on the same area and the same infectious,ρ is a constant)[2].

$$\frac{\mathrm{d}i}{\mathrm{d}s} = \frac{\rho}{s} - 1 \tag{9}$$

$$i(s) = \rho l N \frac{s}{s_0} - s + s_0 + i_0 \tag{10}$$

Draw its figure:



From this figure, we can see that:

1. regardless of where the phase trajectoriesthe start on, it will eventually intersect with the s axis, that is the patient will eventually disappear;

2. the final uninfected healthy proportion is s_m(when $t \to \infty$);

3. if $s_0 > \rho$, the $i(t)$ first increase, while when $s = \rho$, $i(t)$ reaches a maximum:
$$i_m = s_0 + i_0 - \rho(1 + lN\frac{s_0}{\rho})$$
Then, $i(t)$ decreases and tends to zero, $s(t)$ is monotonically reduced to s_m.

4. If $s_0 < \rho$ then $i(t)$ decreases monotonically to 0, $s(t)$ decreases monotonically to s_m.

The following study relationship between Ebola virus spread and time of begin taking isolation.

The figure below is based on Figure 2 with changeing the time when start taken to isolate, when l will increase. Figure 3(B) is the effect of different time of begin taking isolation for the number of patient, $1, 2, \cdots, n$ hour corresponding image by the bottom-up.(MATLAB code for this part is in Appendix 1, 3 and 4)

Figure 3(A) shows that as time goes by, the chart changes from intensive curve to spares curves, which means the infected cases will not increase greatly within a certain period once the initial infection occurs. However, as the isolation delays, the number of infected people increase sharply. As can be seen from Figure 3(B), when began to take isolated relatively in short time , the maximum number of infections is relatively small, but with a long time, the sharp increase in the number of infections. So once found infected should be isolated as soon as possible, in 4h hours of isolation is ideal, relatively small number of infections infected by per patient [3], but if it start take isolation than 11h, then the consequences will not optimistic, each patient infects a lot of people.

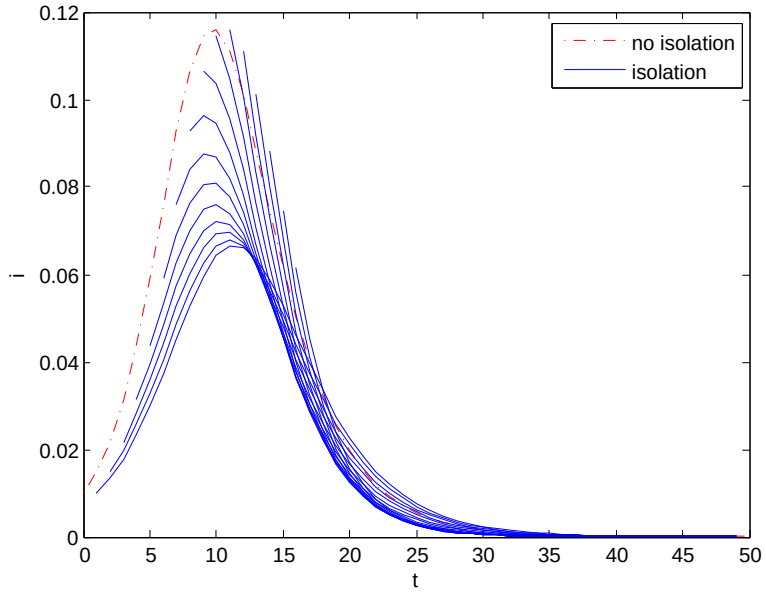
3.2 Required Drug

Symbol definition:

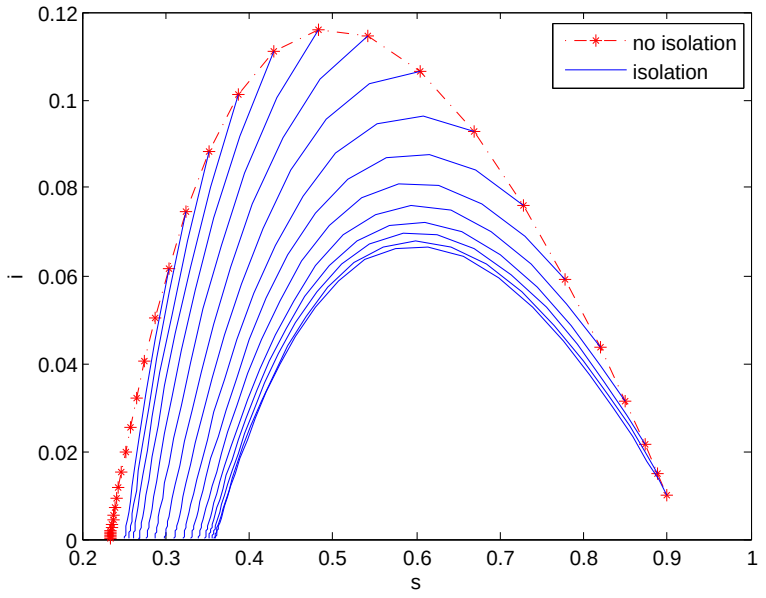
p_0	In the cure range, the maximum dosage required to cure each Ebola patient.
$Q(t)$	The amount of drug at time t.

Assumptions:

1. The Ebola virus has no variation in the present period.



(A)

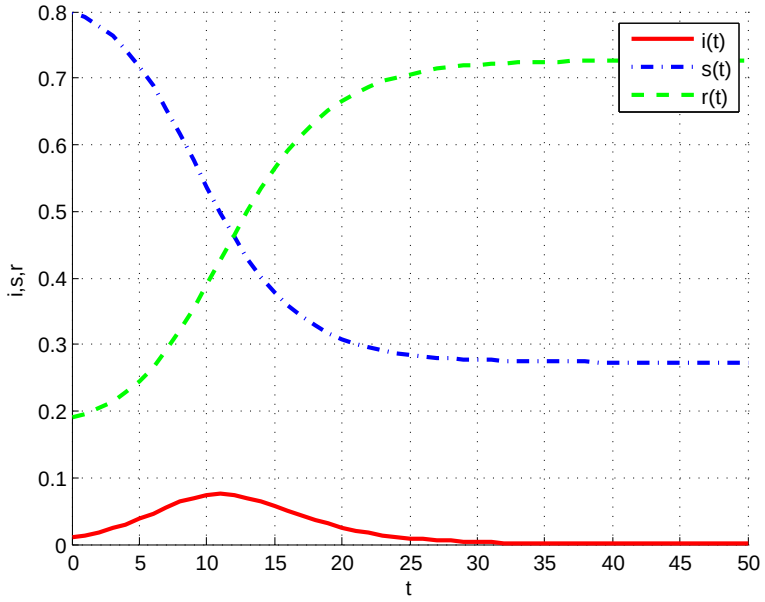


(B)

Figure 3: The effect of different time of begin taking isolation for spread.

The amount of the drug required to $Q(t) = p_0 * i(t)$.

The figure for $i(t)$ in Case 2 shown as below:



The amount of drug $Q(t)$ can be calculated is p_0 times of $i(t)$, $Q(t)$ change with t similar to i change with t.

3.3 Transportation System

Symbol definition:

$v(t)$	The speed of the drug production at moment t.
v_0	Transportation speed.
A_i	Drug production places.
B_j	Drug demanded place.
a_i	Producting speed of A_i.
b_j	Demand of B_j.
x_{ij}	The quantity transport from A_i to B_j.
s_{ij}	the transportation path length from A_i to B_j.
$i = 1, 2, \cdots, m; j = 1, 2, \cdots, n$	

Assumptions:

1. The number of patients increase with time in the short term, to make patients whose illness is not serious can be cured, the speed of the drugs production $v(t)$ needs increasing with time.

2. Drug delivery using the same kind of transportation and transportation speeds v_0 are consistent.

3. There are m production places $A_1, A_2, \cdots, A_m$ for the drug,the producting speed for the drug of A_i is a_i,$i = 1, 2, \cdots, m$.There are n places $B_1, B_2, \cdots, B_n$ need the drug,the demand of B_j is b_j,$j = 1, 2, \cdots, n$.

4. $\sum_{i=1}^{m} a_i = \sum_{j=1}^{n}$.For all $i \in \{1, 2, \cdots, m\}$ and $j \in \{1, 2, \cdots, n\}$, have $a_i, b_j > 0$.

Modeling and solving:
Drug production time $t = \frac{x_{ij}}{v(t)}$, drug transportation time $t' = \frac{s_{ij}}{v_0}$, let $c_{ij} = \frac{1}{v(t)}$, then:

$$\min t'' = \sum_{i=1}^{m}\sum_{j=1}^{n}(t + t') = \sum_{i=1}^{m}\sum_{j=1}^{n} c_{ij}x_{ij} + \sum_{i=1}^{m}\sum_{j=1}^{n} t' \tag{11}$$

$$s.t. \begin{cases} \sum_{j=1}^{n} x_{ij} = a_i, i = 1, 2, \cdots, m \\ \sum_{i=1}^{m} x_{ij} = b_j, j = 1, 2, \cdots, n \\ x_{ij} \geq 0, i = 1, 2, \cdots, m, j = 1, 2, \cdots, n \end{cases}$$

where $\sum_{i=1}^{m}\sum_{j=1}^{n} t'$ is certain, we just calculate the minimum of $\sum_{i=1}^{m}\sum_{j=1}^{n} c_{ij}x_{ij}$.
Let:

$$x = \begin{pmatrix} x_{1,1} & x_{1,2} & \cdots & x_{1,n} \\ x_{2,1} & x_{2,2} & \cdots & x_{2,n} \\ \vdots & \vdots & \ddots & \vdots \\ x_{m,1} & x_{m,2} & \cdots & x_{m,n} \end{pmatrix}$$

$$C = \begin{pmatrix} c_{1,1} & c_{1,2} & \cdots & c_{1,n} \\ c_{2,1} & c_{2,2} & \cdots & c_{2,n} \\ \vdots & \vdots & \ddots & \vdots \\ c_{m,1} & c_{m,2} & \cdots & c_{m,n} \end{pmatrix}$$

$$b = \begin{pmatrix} a_1 & a_2 & \cdots & a_m & b_1 & b_2 & \cdots & b_n \end{pmatrix}$$

$$A = \begin{pmatrix} a_{1,1} & a_{1,2} & \cdots & a_{1,n} \\ a_{2,1} & a_{2,2} & \cdots & a_{2,n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{m,1} & a_{m,2} & \cdots & a_{m,n} \end{pmatrix}$$

where $a_{ij} = e_i + e_{m+j}$, e_i is a column vector with $m + n$ elements, and i-th element is 1, otherwise 0. Then we have:

$$\min t = Cx$$

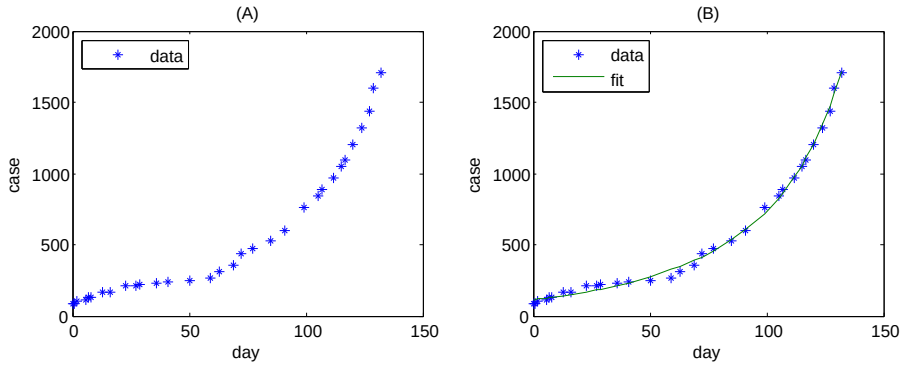


Figure 4: Statistic data and fitting

$$s.t. \begin{cases} Ax = b \\ x \geq 0 \end{cases}$$

when $\sum_{j=1}^{n} x_{ij} = a_i$ [4], we can ensure the availability of drugs in different place.

3.4 Produnction Speed

Symbol definition:

x_{ij}	The quantity transport from A_i to B_j.
$v(t)$	The speed of the drug production at moment t.
t	Time in production.
t'	Time in transportation.
$i = 1, 2, \cdots, m; j = 1, 2, \cdots, n$	

$v(t) = \frac{x_{ij}}{t''-t'}$, according to the formula, to obtain the shortest production and transportation time $t''(t'' > t')$, we can find the maximum production speed.

4 Testing and Analysis

4.1 Model Testing

Now take cases infected with Ebola in the distribution of West African countries as an example [5](data see Appendix 6), by each set of data, the number of days as the horizontal and the number of infections to the vertical axis, to make a scatter plot, as shown in Figure 4(A). Using MATLAB Statistics Toolbox function nlinfit, fitting

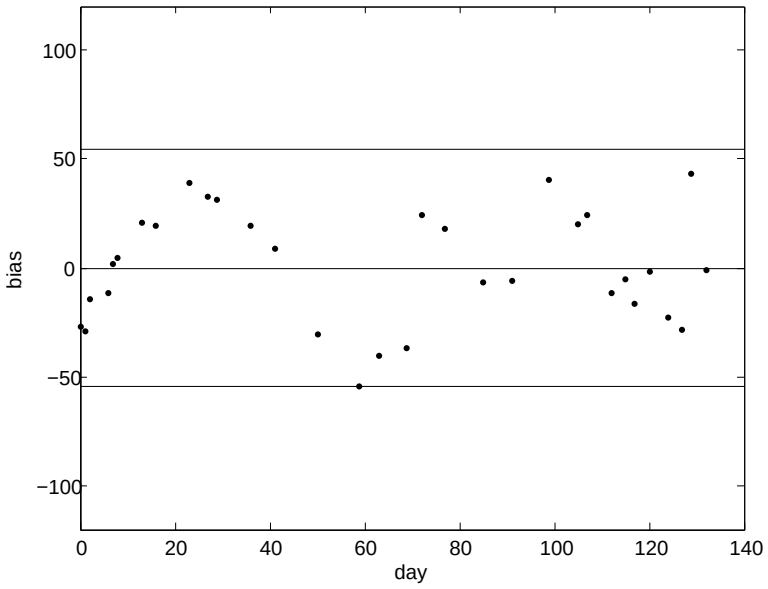


Figure 5: Bias analyze.

formula according to data:

$$i(t) = 113e^{0.01748t} + 0.2253e^{0.05946t} \tag{12}$$

The formula in line with graphs for Ebola virus infection early on the case 2 in Section 3.1, from Figure 4(B) we can see the data fit with good results. It show that these assumptions and models introduced is appropriate.

4.2 Model Analysis

Analyze data on the distribution of infection cases by Ebola in the West African countries and make fitting bias figure, as shown in Figure 5.

As can be seen from Figure 5, the error branch points are concentrated in the interval $[-55, 55]$, so fitting fine, it shows that the function above in line with the increasement trend of infectious diseases on beginning, the model has good fidelity.(MATLAB code for this part is in Appendix 5)

5 Model Evaluation

5.1 Advantage

- This model gives a result of a general, not only for Ebola virus infection case analysis, but also for other infections virus analysis.
- Model use a method of combination of numbers and shapes to present Ebola virus propagation visually objectively.
- Model not only takes into account more than two origin, more requirements to the case but also combines drug production speed with drug delivery speed to get the optimal allocation scheme.
- The model takes into account the recovered cases and death (no more infection) and greatly improve the predictability and applicability of the model.
- The principle of the model is straightforward. It simplify algorithm. Model has good practicability.

5.2 Weaknesses

- The study population N is the total number of dynamic change, there is birth, death, flow and so on. This makes the model and the actual situation have a tolerance.
- Ebola virus in the human body have latency and Ebola virus carriers is not contagious, and this is where the model is not perfect.
- Drug has half-life in human body. Patients must adhere to medication for some time to recover, so the dose calculations and the actual have a tolerance.
- Several factors are not taken into account, such as technology level of every medicine manufacturer, the different production rate and difference in transport vehicle, road condition, which might result in the gap between optimal distribution plan and the reality.
- In actual circumstances, defective medicines in production, in transport and in medicine-taking will affect the reliability of the model.

5.3 Improvement and Value of the Model

In the process of model predictions, program one in Model One ignores many factors, does not comply with the later development of Ebola virus infection. Based on program one, we consider more factors and then establish program two. Development of Ebola virus infection and the development of other infections were similar. However we know that both the use of drug and isolation measures for Ebola virus infection trend have important effect. Therefore, our model can give a more comprehensive account of multiple factors and address the real problems. In other words, the model prediction in the number of infections is accurate, but due to virus variation and other uncontrollable factors, it might not be predicable in the long period. To develop in line with the actual situation of the Ebola virus-term forecast, we must improve the above model further.

Model Two are simplified in many factors, so our model should consider all factors affecting the transport logistics and distribution, but the reality is very complex,multifaceted consideration is needed to improve our model of development direction.

Generally, infection intensity can be perceived through the new added cases between intervals yet the infection trend can hardly be determined. The model we build can solve the problem and present a clearer picture of the transmission and seize the best time to quarantine. In terms of distribution and transport, our model can calculate the shortest time of transport and production, hence saving more time and life by providing medicine to disease-stricken areas. Our model can be applied not only to the establishment of the Ebola virus, but also be applied to a virus similar to Ebola.

6 A Letter for the World Medical Association

A letter for the World Medical Association

Dear the World Medical Association:

Thanks to the world medical association has manufactured a new medication for the treatment of Ebola virus to control the spread of Ebola, more and more patients can be treated. In order to make better use of the medication, we also need to optimize the amount of drugs, drug distribution transportation systems, drug production speed.

According to our research, we got two findings from our research and modeling. In terms of the trends of Ebola virus infection,

we find that Ebola cases will continue to increase dramatically if no control is made at early stage, but infection can be control if prevention is made such as therapeutic agents. When drug application is optimized, infection will cease, even decline. Also, the infection will spread only when the number of infected cases is over a certain threshold. That's why Ebola transmit more rapidly in those densely-populated areas, where prevention is poorly managed and excluding rate is high. Reversely, Ebola can be better controlled in less populated areas with a lower infection rate. In terms of drug dosage, we must make sure sufficient medicine supply for early infected patients but avoid possible wastes. The dosage of most severe cases is used as the base and multiplied by the number of patients. The calculated result is the best dose.

We also studied the best drug distribution transport systems. The purpose is to guarantee the amount of medicine for each infected areas and fast acquisition of the medicine. Given that the needed amount and production volume is constant, we calculate the minimum time for medicine production and the amount of time for distribution. This is the best distribution plan that can save more time and lives. Regarding the production rate, the amount of needed medicine divided the time spent in production is the best production rate. Mentioned above is the result of our study. We hope that the World Medical Association will seriously consider and adopt the results of our study, and show an announcement on better optimize the use of drugs in order to do a better job in the fight against Ebola!

Our team wishes Ebola patients can recover rapidly and people all around the world are happy and healthy!

Team #38403
February 9, 2015

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[6] Shaohui Zhang, The mathematical model, Science Press(August 2010)

Appendix

1.MATLAB code for function ill (ill.m):

```
function y = ill(t,x)
k=1;l=0.5;
y=[k*x(1)*x(2)-l*x(1);-k*x(1)*x(2)];
end
```

2.MATLAB code for solve ill (sill.m):

```
ts=0:50;
x0=[0.01;0.80]
[t,x]=ode45('ill',ts,x0);[t,x]
figure(1);clf;hold on;
plot(t,x(:,1),'-r','LineWidth',2);
plot(t,x(:,2),'-.b','LineWidth',2);
plot(t,1-x(:,1)-x(:,2),'--g','LineWidth',2);
xlabel('t');ylabel('i,s,r');
legend('i(t)','s(t)','r(t)');grid on;%pause
figure(2);
plot(x(:,2),x(:,1),'LineWidth',2);
xlabel('s');ylabel('i');
legend('i(s)');grid on;hold off;
```

3.MATLAB code for function ill2 (ill2.m) when taken isolution:

```
function y = ill2(t,x)
k=1;l=0.6;
y=[k*x(1)*x(2)-l*x(1);-k*x(1)*x(2)];
end
```

4.MATLAB code for study the effect of different time of begin taking isolation for spread:

```
dur=50;
ts=0:dur;
x0=[0.01;0.90];
figure(1);
[t,x]=ode45('ill',ts,x0);
plot(t,x(:,1),'r-.');
xlabel('t');ylabel('i');
hold on;
figure(2);clf;
plot(x(:,2),x(:,1),'r*-.');
hold on;
for g=1:(dur/3)
    [t,xx]=ode45('ill2',ts((g+1):dur),x(g,:));
    figure(1);
    plot(t,xx(:,1));
    figure(2);
    plot(xx(:,2),xx(:,1));
end
xlabel('s');ylabel('i');
legend('no isolation','isolation');
hold off;
figure(1);
legend('no isolation','isolation');
hold off;
```

5.MATLAB code for statistic data and fitting:

```
t=load('day_sum.txt');
s=load('sum_dat.txt');
f=@(b,t)b(1)*exp(b(2)*t)+b(3)*exp(b(4)*t);
[b,r1]=nlinfit(t,s(:,1),f,[113 0.01748 0.2253 0.05946]);
% 113*exp(0.01748*t)+0.2253*exp(0.05946*t)
figure(1);clf;
subplot(1,2,1);
```

```
plot(t,s(:,1),'*');
legend('data','Location','NorthWest');
xlabel('day');ylabel('case');
title('(A)');
subplot(1,2,2);
plot(t,s(:,1),'*',...
    t,b(1)*exp(b(2)*t)+b(3)*exp(b(4)*t),'-');
legend('data','fit','Location','NorthWest');
xlabel('day');ylabel('case');
title('(B)');
figure(2);clf;
plot(t,r1,'k.',[0,140],[0,0],'k',...
    [0,140],[min(r1),min(r1)],'k',...
    [0,140],[-min(r1),-min(r1)],'k');
axis([0 140 -120 120]);
xlabel('day');ylabel('bias');
%title('Bias');
```

6.Statistic data [5]**:**

Date	Cases
2014/3/26	1603
2014/3/27	1440
2014/3/31	1323
2014/4/1	1201
2014/4/2	1093
2014/4/7	1048
2014/4/10	964
2014/4/17	888
2014/4/21	844
2014/4/23	759
2014/4/30	599
2014/5/5	528
2014/5/14	474
2014/5/23	438
2014/5/27	354
2014/6/2	309
2014/6/5	270
2014/6/10	245
2014/6/18	243
2014/6/24	233
2014/7/2	220
2014/7/8	215
2014/7/10	209
2014/7/15	169
2014/7/18	163
2014/7/20	135
2014/7/23	130
2014/7/27	114
2014/7/30	103
2014/8/1	86
2014/8/4	86