For office use only	Team Control Number	For office use only
T1 _____	**32692**	F1 _____
T2 _____		F2 _____
T3 _____	Problem Chosen	F3 _____
T4 _____	**A**	F4 _____

2015

Mathematical Contest in Modeling (MCM/ICM) Summary Sheet

We take the bottom-up approach and build a system model containing epidemic regions and medicine and vaccine manufacturers. Strategies for production and distribution are designed and tested. Mathematical criterions are suggested for evaluating how well each strategy works in eradicating Ebola. We figure out optimal strategy under different settings.

We draw inspiration from the famous SEIR model to build an epidemic region model. However, we take into account the “contact-infection” principle and the variance of resistance among individuals. The refined version also considers the social circle of a person. Simulation results are compared with true data in two African countries to verify its correctness.

Our system model is based on epidemic region model. In specific, the system is implemented as three medical and vaccine providing regions and three epidemic regions. Currently two medicines (ZMapp and JK-05) and one vaccine (VSV-EBOV) are produced in three different countries. It can be seen our model is close to reality.

We study the situation when supply is adequate or not for demand. Under each situation, a number of strategies are applied. A synthesized index containing expense, patients number, cure rate and prevention rate is proposed for effective appraisal of strategies. Best strategies are suggested on each condition.

In sensitivity analysis, we find out four key factors in controlling Ebola. They are the number of people a patient meets per unit time, the probability that a patient goes to hospital, the speed medicine and vaccine are produced and how they are distributed. Other elements, such as public awareness and population density, are also discussed.

We wish our work may help in real-life fight against Ebola.

Say Goodbye to Ebola

Introduction

Since the outbreak of Ebola in Guinea last spring, the epidemic has rapidly spread to neighboring countries and claimed a vast number of lives. To eradicate, or at least put the disease under control, a model is in urgent need to determine how vaccine and medicine should be produced, transported and distributed. In this paper, we simulate a system of medicine and vaccine manufacturers and epidemic regions. By designing strategies and applying them to different situations, we find reasonable strategies to distribute medicine and vaccine. We believe our results will help eradicating Ebola in real life.

Restatement of the problem

We are required to build a mathematical model to describe the process of curbing Ebola, which includes critical factors such as the spread of disease and the distribution of medicine. Therefore, we have four sub-problems:

1) Build a model that can simulate the epidemic area.
2) Figure out how these factors act in the model.
3) Propose mathematical criteria for the performance of a control method.
4) Find a control method that reaches best effect.

Literature Review

Joshua S. Weitz [2014] has built a model to describe the spread of Ebola virus on the basis of SEIR model. In SEIR model, people in an epidemic area are classified into four types, namely, S (susceptible), E (exposed individuals in the latent period), I (infected) and R (recover with immunity). The model assumes that:

1) The system is closed.
2) The length of latent period and probability of death is same for every patient.
3) The probability of being infected is same for every healthy individual.
4) The number of people a patient meets per unit time is constant.

The SEIR model is represented with a system of four linear differential equations.

$$\begin{cases} S' = \Lambda S - \mu S - \lambda S \\ E' = -(\mu + \alpha)E + \lambda S \\ I' = -(\mu + \gamma)I + \alpha E \\ R' = -\mu R + \gamma I \end{cases}$$

In the system, Λ is the birth rate, μ is the death rate, γ is the probability a

patient gets cured, α is the probability a carrier becomes a patient and λ is the probability a healthy person gets infected. It can be re-written in matrix form as:

$$\frac{d}{dt}\begin{bmatrix} S \\ E \\ I \\ R \end{bmatrix} = \begin{bmatrix} \Lambda-\mu-\lambda & 0 & 0 & 0 \\ \lambda & -(\mu+\alpha) & 0 & 0 \\ 0 & \alpha & -(\mu+\gamma) & 0 \\ 0 & 0 & \gamma & -\mu \end{bmatrix}\begin{bmatrix} S \\ E \\ I \\ R \end{bmatrix}$$

SEIR model is concise and classic. However, it does not suit our case for several reasons. Firstly, it ignores the difference of resistance and course of disease between people. Secondly, it fails to consider in detail how infection happens. Thirdly, it mainly focuses on the linear part of the dynamic system. Therefore, it can ideally predict long-term performance of an epidemic region, but fails to capture show-term performance, which is essential in comparing different control methods.

Characteristics of Ebola

Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever, is a severe illness in humans with high fatality rate. To precisely describe the condition in epidemic area, following characteristics of Ebola are used.

1) Fatality rate is between 50% and 90%.
2) Latent period can extend to 21 days, but it usually ranges from 5 to 10 days.
3) Ebola is not highly contagious since it is transmitted through blood and body fluid.
4) Patients in latent period cannot infect others.
5) Those recover from Ebola will have lifelong immunity.
6) People ages between 16 and 59 are more vulnerable to the virus.

Assumptions and Justifications

1) The infection of Ebola only happens between person and person. Although most primates are susceptible to Ebola, few people in real life contact these animals.

2) The epidemic area is closed; nobody enters or leaves the system. Epidemic areas will strictly control the entry and exit of aliens.

3) The dead has no influence on the system. The corpses are supposed to be not infectious.

The Eradicating Ebola Model

The first task is to set up an epidemic region model. We draw inspiration from the SEIR model and take into consideration those characteristics of Ebola virus, ending up with a refined version of SEIR model. To study the short-term performance in an epidemic region, the non-linear part in the system of differential equations, that is the

$f(t)$ in $\frac{dx}{dt} = Ax + f(t)$, cannot be discarded. However, the explicit form of $f(t)$ is unknown. As a result, we simulate the epidemic region on microscopic level. In specific, the epidemic region is viewed as a set of people. Each person in the set has attributes like health state, resistance and latent period. The process of infection is imitated through interaction between healthy and sick people.

The second task is to build a distribution model of vaccine and medicine on the basis of the epidemic region model. It is implemented as a complex system of producers of vaccine or medicine and epidemic regions. Taking advantage of this big model, we can adjust parameters like the production rate, transportation cost and distribution strategies to observe how these factors work in real-life fight with Ebola.

Symbol Table

Symbol	Definition	Units
	Symbols for SEIR	
$\mu_{\text{resistance}}$	Expectation of individuals' resistance	Dimensionless
$\sigma^2_{\text{resistance}}$	Variance of individuals' resistance	Dimensionless
μ_{death}	Expectation of individuals' probability of death	Dimensionless
σ^2_{death}	Variance of individuals' probability of death	Dimensionless
T_{latent}	Maximum length of latent period	Day
T_{lethal}	Maximum length of lethal period	Day
$R^{(i)}$	Resistance of individual i	Dimensionless
$P^{(i)}_{\text{death}}$	Death rate of individual i	Dimensionless
$t^{(i)}_{\text{carry}}$	Time when individual i shift from healthy to carrier	Day
$t^{(i)}_{\text{Infected}}$	Time when individual i shift from carrier to infected	Day
$t^{(i)}_{\text{death}}$	Time when individual i shift from infected to dead	Day
$P_{\text{quarantine}}$	The probability of an Ebola patient goes to hospital	Dimensionless
$\lambda^{(k)}$	Natural growth rate of epidemic region k	Dimensionless
$NF_{contact}$	Number of people a free person meets per day	Person

$NI_{contact}$	Number of people an insulated person meets per day	Person
$N_{health}^{(k)}$	Number of healthy individuals in area k	Person
$N_{carrier}^{(k)}$	Number of carriers in area k	Person
$N_{sick}^{(k)}$	Number of sick people in area k	Person
$N_{cured}^{(k)}$	Number of individual cured in area k	Person
	Symbols for Drug	
$V^{(j)}$	Production rate of drug j	Serving per day
$C^{(j)}$	Production cost of drug j	Dollar
$S^{(j)}$	Stock of drug j	Serving
	Symbols for Transportation	
$d_{(j)}^{(k)}$	Distance for sending drug j to epidemic region k	Hour
$TC_{(j)}^{(k)}$	Transportation expense for sending drug j to epidemic region k	Dollar
$ND_{(j)}^{(k)}$	Quantity demand of drug j in epidemic region k	Serving
$LC_{(j)}^{(k)}$	Loss coefficient of drug j in affected area k	Serving

Assumptions of the Epidemic Region Model

1) The epidemic region is a closed system.

2) The length of latent period and lethal period (the time interval between getting infected and death) follows uniform distribution.

3) The number of people a person meets is in proportion to the density of population. Those who are insulated meet less people than those who are free every day, since the social circle of the former group are restricted to doctors, nurses and other patients.

4) The time interval between getting infected and being quarantined is determined by the region's medical condition.

5) The demand for medicine and vaccine of each epidemic region in the distribution model is based on the result of simulation.

6) The cost of transportation is only related to the amount of goods and the distance.

Four Types of People

We categorize people in four types as followed:

1) Healthy: not infectious, susceptible to virus, but will not become carriers without contact with Infected.

2) Carrier: not infectious, but will become carriers after a certain amount of time.

3) Infected: infectious, will become Dead or Cured after a certain amount of time.

4) Cured: not infectious, permanently immune to the virus.

Two Groups of People

People are classified into two types, free and insulated.

1) Free people contains those who are healthy, those who carry the disease, those are infected but are not in quarantine and those who are cured.

2) Insulated people include contains those who are infected and are in quarantine.

Conversion Rules between Four Types of People and Two Groups

1) A person in an epidemic region has resistance $R^{(i)}$, which is between 0 and 1. When a healthy person meets an infected person, the probability he gets infected is: $P_{\text{inf ected}}^{(i)} = 1 - R^{(i)}$

2) The latent period of a Carrier follows uniform distribution of $U(0, T_{\text{latent}})$. After this period, the Carrier becomes an Infected person.

3) The lethal period of an Infected person follows uniform distribution of $U(0, T_{\text{lethal}})$. After this period, the probability that he dies is P_{death}; the probability that he becomes a Cured person is $(1 - P_{\text{death}})$.

4) After a Carrier becomes an Infected person, every day the probability his state changes from Free to Insulated is P_{shift}. Once he enters the Insulated group, he will not leave unless he dies or is curd.

5) A Cured person will never be infected again.

6)Every day a person in Free group will randomly meet $NF_{contact}$ people; a person in Insulated group will randomly meet $NI_{contact}$ people.

The Refined Epidemic Region Model

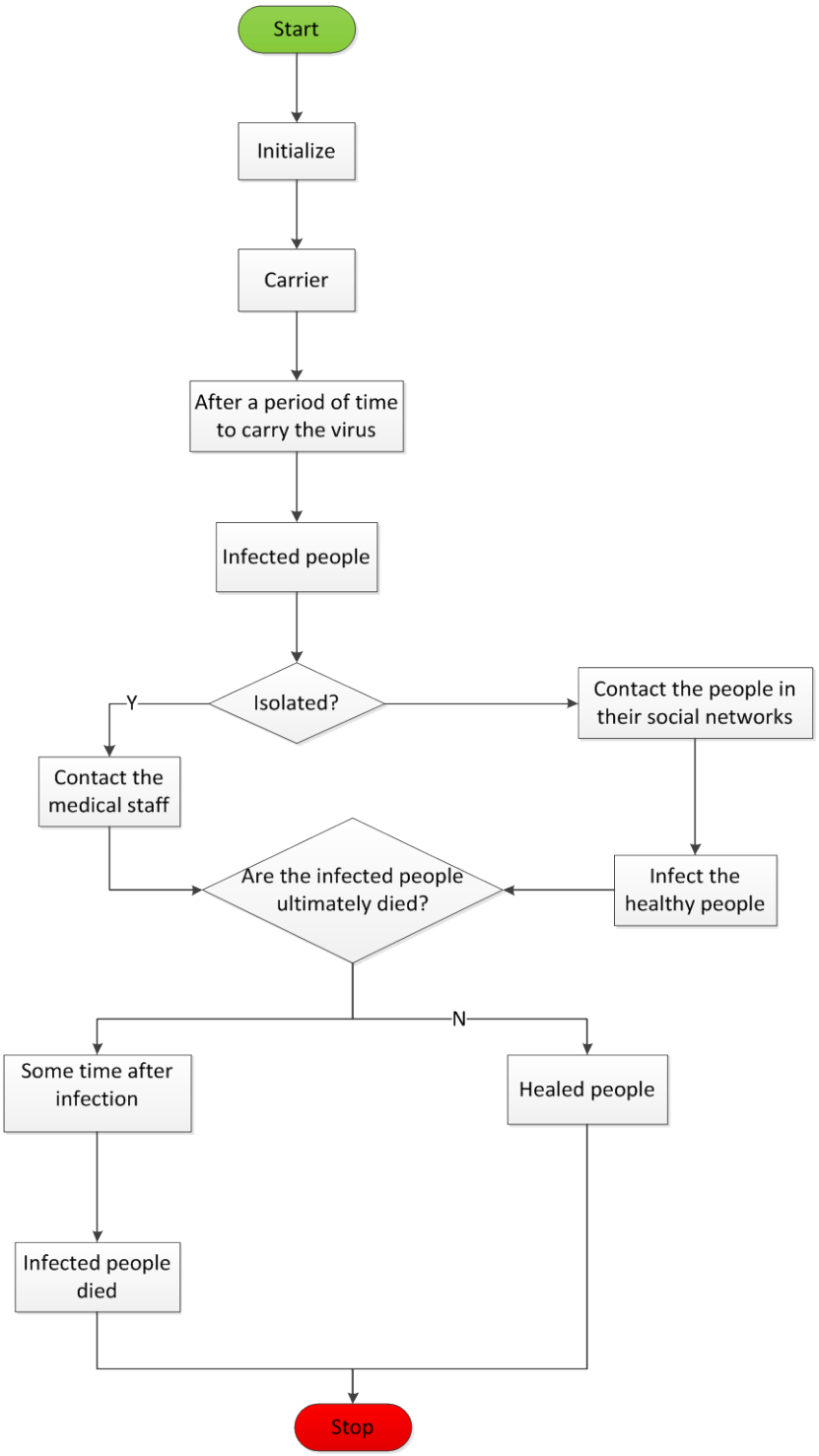
We consider the following three points and improve the original model.

1) Natural growth rate λ: since we are interested in short-term behavior, it is assumed that only healthy people will reproduce.

2) The distribution of latent period and lethal period: with accordance to reports, the lengths of these two periods are primarily concentrated in a certain center. Therefore we treat it as a Gaussian random variable, which means that:

$$t_{latent} \sim N(\mu_{latent}, \ \sigma^2_{latent}), \ t_{lethal} \sim N(\mu_{lethal}, \sigma^2_{lethal})$$

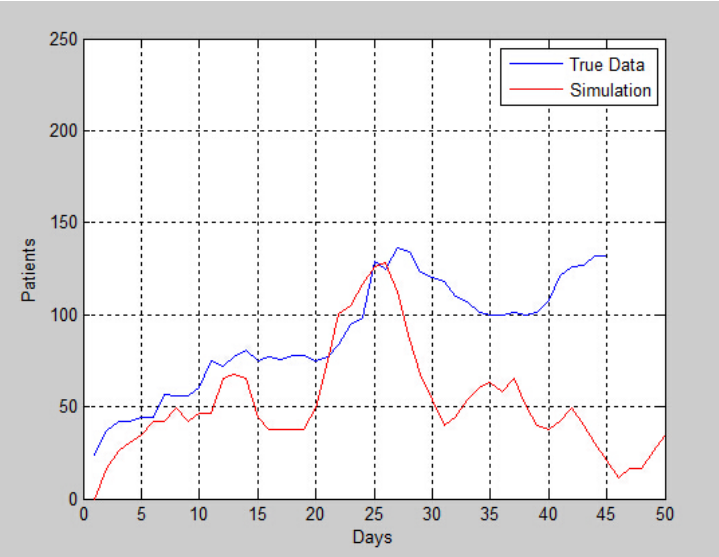
3) The social network of people: in reality, each individual has his own social circle. In most cases he only meets those in the circle. In the refined model, we build one social network for Free group and another for Insulated group. A person's social circle also changes when he shifts between two groups.



Model Validation

We verify the correctness of our epidemic region model by comparing the simulation results with true data.

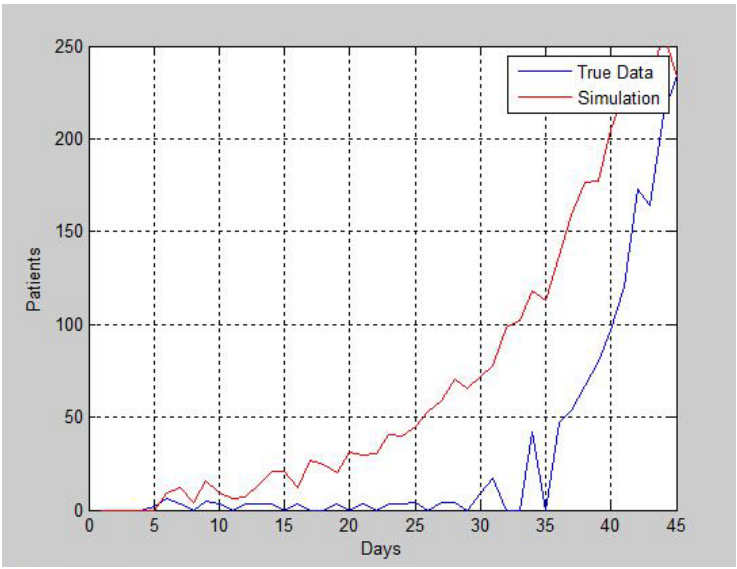
1）Guinea (April, 2014 ~ August, 2014)



Error Analysis:

In our simulation result, the number of patients reaches its peak at about 25 days, then it will gradually decreases. True data on the whole agrees with simulation result before 30 days, but it does not decrease as predicted. According to reports from CNN, at that time another source of infection is discovered, which causes the polyline to continue going up after 25 days.

2）Liberia (April, 2014 ~ August, 2014)



Error Analysis:

In our simulation result, there ought to be over 100 patients at 30 days or so. But true data shows the patients number is relatively low, but erupts at about 35 days. We guess that is due to low awareness of Ebola. There were already many patients at that time, but they did not go to hospital, so they were not discovered, which led to the phenomenon that few people were infected by 30 days but the number grew rapidly in just a week.

The Distribution Model

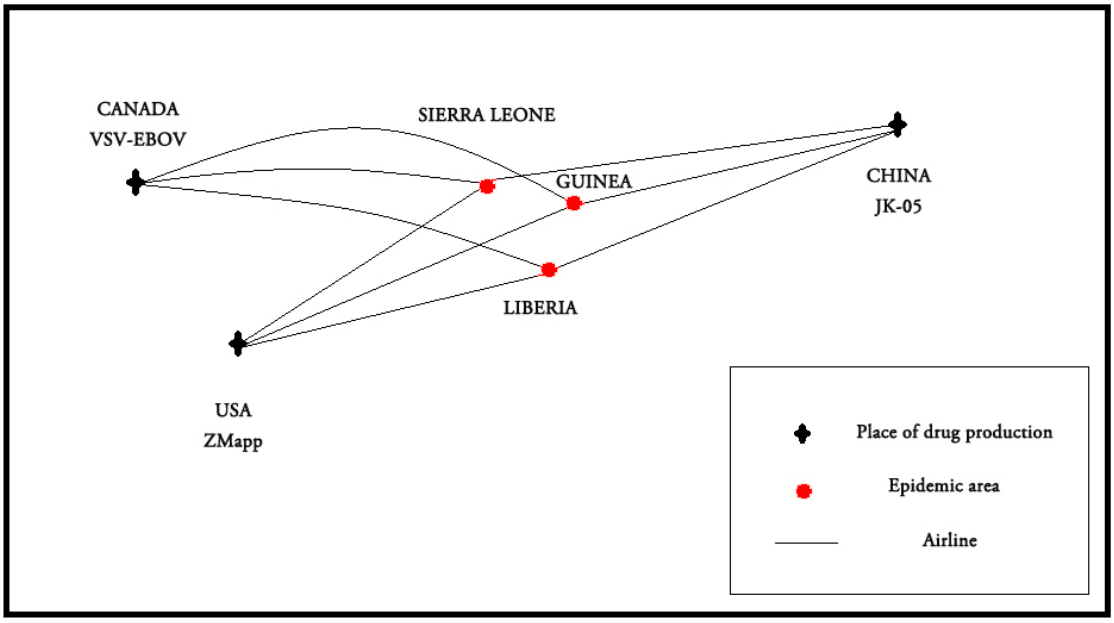
According to online information, currently one kind of vaccine and two kinds of medicine are manufactured in three different countries, each having different effect. It is elaborated in the producers' form.

Name	ZMapp	JK-05	VSV-EBOV
Type	Medicine	Medicine	Vaccine
Cost	High	Medium	Low
Speed of Production	Slow	Quick	Quick
Effect	100% works in 24 hours; 50% works in 48 hours	100% works in 48 hours	100% works

Besides, the main victims of Ebola are all African countries, and we choose Guinea, Libya and Sierra Leone. Their conditions are displayed in the receivers' form.

	Number of Patients	Number of Dead
Guinea	2975	1944
Liberia	8745	3746
Sierra Leone	10740	3276

It can be seen that our model is quite close to reality. Therefore, our distribution model is a system of three providers and three receivers.



Distribution Strategies for Medicine

We have designed and tested following four strategies for distributing medicine:

1) Minimal Distance: a provider first satisfies the receiver closest in distance;
2) Maximal Demand: a provider first satisfies the receiver that requires the greatest amount of medicine;
3) Minimal Demand: a provider first satisfies the receiver that requires the smallest amount of medicine;
4) Latest Outbreak: a provider first satisfies the receiver whose outbreak of disease happens latest.

Distribution Strategies for Vaccine

Since vaccine and medicine work in different way, we have also designed and tested following four strategies for distributing vaccine:

1) Minimal Distance: same as above
2) Worst Condition: a provider first satisfies a receiver having greatest number of patients;
3) Best Condition: a provider first satisfies a receiver having smallest number of patients;
4) Medical Clerk First: refined version of Minimal Distance, a provider first satisfies medical clerk belong to the receiver.

Evaluation Criterion

To find effective criterion, we choose four indexes for evaluation, total expense $C_{\text{total}}^{(i)}$, total number of patients $N_{\text{sick}}^{(i)}$, effect of treat $R_{\text{cure}}^{(i)} = \dfrac{number\ of\ \ patients}{total\ number}$ and

effect of prevention $R_{\text{prevention}}^{(i)} = \dfrac{number\ of\ susceptible}{total\ number}$. The appraisal procedure can be illustrated in four steps:

1) Determine judging vector for each distribution strategy:

$$W^{(i)} = \left[C_{\text{total}}^{(i)} \ N_{\text{sick}}^{(i)} \ R_{\text{cure}}^{(i)} \ R_{\text{prevention}}^{(i)} \right]^T$$

2) Normalize the judging vector:

$$NW^{(i)} = \left[\frac{C_{\text{total}}^{(i)}}{\max(C_{\text{total}}^{(i)})} \frac{N_{\text{sick}}^{(i)}}{\max(N_{\text{sick}}^{(i)})} R_{\text{cure}}^{(i)} \ R_{\text{prevention}}^{(i)} \right]^T$$

3) Calculate the norm of each normalized judging vector:

$$d^{(i)} = \left\| NW^{(i)} \right\| = NW^T \bullet NW$$

4) Choose the judging vector with the smallest norm. The corresponding strategy is the best.

With regard to life experience, the above criterion considers almost all respects in terms of evaluating how well a distribution strategy works. And the better a strategy is, the smaller the norm of its normalized judging vector will be.

Verification of the Criterion

To figure out the influence of the speed of manufacture on different strategies, we discuss two situations: supply is adequate and is inadequate.

1) Distribution Strategies for Medicine

A. Supply is inadequate

Strategy	$C_{\text{total}}^{(i)}$	$N_{\text{sick}}^{(i)}$	$R_{\text{cure}}^{(i)}$	$R_{\text{prevention}}^{(i)}$
Minimal Distance	0.8147	0.8324	0.1575	0.2572
Maximal Demand	0.9058	1.0000	0.3649	0.3854
Minimal Demand	1.0000	0.7785	0.2576	0.3003
Latest Outbreak	0.8434	0.7469	0.1506	0.2419

The distance matrix is $D = \begin{bmatrix} d^{(1)} \\ d^{(2)} \\ d^{(3)} \\ d^{(4)} \end{bmatrix} = \begin{bmatrix} 1.2032 \\ 1.4499 \\ 1.3276 \\ 1.1621 \end{bmatrix}$

$\therefore$ Latest Outbreak is the BEST strategy when supply is inadequate.

B. Supply is adequate

Strategy	$C_{\text{total}}^{(i)}$	$N_{\text{sick}}^{(i)}$	$R_{\text{cure}}^{(i)}$	$R_{\text{prevention}}^{(i)}$
Minimal Distance	0.7218	1.0000	0.1787	0.2555
Maximal Demand	0.7157	0.6357	0.1977	0.1912
Minimal Demand	1.0000	0.9491	0.1831	0.2060
Latest Outbreak	0.8595	0.8340	0.1922	0.2318

The distance matrix is $D = \begin{bmatrix} d^{(1)} \\ d^{(2)} \\ d^{(3)} \\ d^{(4)} \end{bmatrix} = \begin{bmatrix} 1.5458 \\ 1.9960 \\ 1.4060 \\ 1.2349 \end{bmatrix}$

∴ Maximum Demand is the BEST strategy when supply is adequate.

2) Distribution Strategies for Vaccine

A. Supply is inadequate

Strategy	$C_{\text{total}}^{(i)}$	$N_{\text{sick}}^{(i)}$	$R_{\text{cure}}^{(i)}$	$R_{\text{prevention}}^{(i)}$
Minimal Distance	0.7769	0.8948	0.1387	0.2669
Worst Condition	1.0000	0.8171	0.1816	0.2898
Best Condition	0.7971	1.0000	0.1955	0.2456
Medical Clerk First	0.8235	0.6944	0.1052	0.2463

The distance matrix is $D = \begin{bmatrix} d^{(1)} \\ d^{(2)} \\ d^{(3)} \\ d^{(4)} \end{bmatrix} = \begin{bmatrix} 1.2226 \\ 1.3359 \\ 1.3168 \\ 1.1100 \end{bmatrix}$

B. Supply is adequate

Strategy	$C_{\text{total}}^{(i)}$	$N_{\text{sick}}^{(i)}$	$R_{\text{cure}}^{(i)}$	$R_{\text{prevention}}^{(i)}$
Minimal Distance	0.8994	0.9551	0.0997	0.1513
Worst Condition	0.9021	0.9626	0.1104	0.1951
Best Condition	0.9760	1.0000	0.0853	0.1060
Medical Clerk First	1.0000	0.7984	0.0738	0.0991

The distance matrix is $D = \begin{bmatrix} d^{(1)} \\ d^{(2)} \\ d^{(3)} \\ d^{(4)} \end{bmatrix} = \begin{bmatrix} 1.3244 \\ 1.3381 \\ 1.4040 \\ 1.2856 \end{bmatrix}$

It can be seen no matter the amount of vaccine is sufficient or not, Medical Clerk First is always the best distribution strategy.

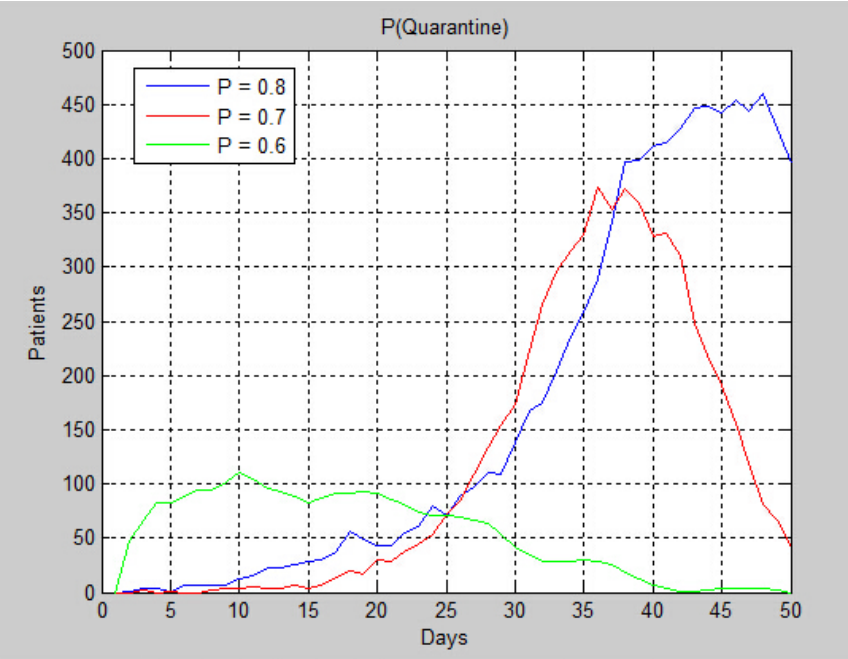
3) Conclusion

	Supply is Adequate?	Strategy
Medicine	True	Latest Outbreak
	False	Maximum Demand
Vaccine	True	Medical Clerk First
	False	Medical Clerk First

Sensitivity Analysis

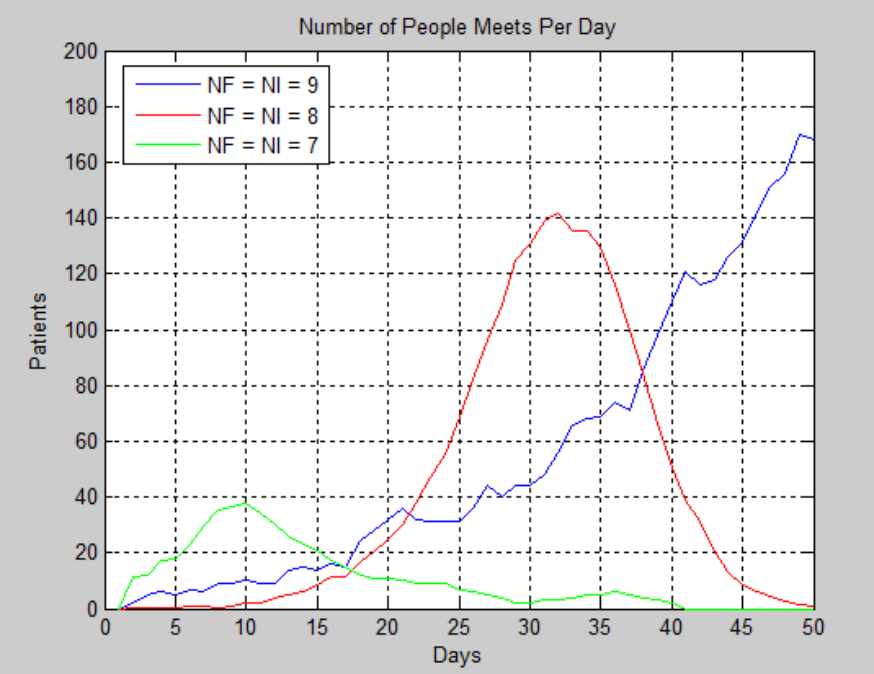
We have made sensitivity analysis of factors in medicine and vaccine distribution, in order to find out which of them play significant role in controlling Ebola.

1) $P_{\text{quarantine}}$: the probability of an Ebola patient goes to hospital and come in quarantine, which reflects the awareness of people and the quality of medical care. In places where people are well-educated and high-quality medical care is available, the probability will be greater, and it will be easier to control Ebola. This is one of the key factors that Ebola is so violent in Africa.



As can be seen in the above picture, when $P_{\text{quarantine}}$ is 0.7, the number of patients finally decreases. By contrast, when $P_{\text{quarantine}}$ is 0.8, the number of patients decreases more quickly; when $P_{\text{quarantine}}$ is 0.6, the number of patients decreases more slowly.

2) $NF_{contact}$ and $NI_{contact}$: the number of people a person in Free group and in Insulated group meets per day. They reflect the density of population of an epidemic region. The denser the population is, the more likely Ebola will spread.



It can be seen from the picture when $NF_{contact} = NI_{contact} = 8$, Ebola patients disappears in the end. But when $NF_{contact} = NI_{contact} = 9$, the disease quickly runs out of control.

3) The constitution of patients: since the two medicines and one vaccine work in differently, they should be distributed to patients to according to how long they have been infected.

Hours after infected	ZMapp	under 24 hours
	JK-05	over 24 hours, but under 48 hours
	DEAD	over 48 hours

4) The production rate: since there are no good medicine or vaccine soon after the outbreak, we have to endure the period during which demand surpass supply before the two come into balance. The amount of medicine and vaccine available will determine which strategy acts best. However, it is clear that controlling Ebola is not controllable until the supply equals or surpasses demand.

Strengths and Weaknesses

Strengths:

1) In sensitivity analysis, we have listed out the key factors in the model, adjusted them separately and observed their influence on simulation result.

2) To adapt our model to acute disease as Ebola, we have considered the function of nonlinear part in the system.

3) We have built a two-level model. The distribution system is based on the epidemic region model, which makes it more reliable and realistic.

4) We have designed and tested a series of strategies in distributing

5) In evaluating the effectiveness of different distribution strategies, we have chosen four indexes and synthesize it into one, which makes it more objective and trustworthy.

Weaknesses:

1) Some of the constants used in the epidemic region model, like probability of infection, are not precise.

2) In distribution model, the frequency of transportation is assumed to be once per day, which may make a difference since 24 hours patients are savable but 48 hours patients undoubtedly will die.

3) The system is considered to be closed. In real life other countries may send medical clerk to offer help.

Further Discussions

With the help of our epidemic region model and producer-receiver system model, the outbreak of diseases can be simulated and predicted effectively. Besides, we are able to simulate distribution strategies of drugs and vaccines, and assess the effect of them. However, limitations and flaws still exist in our models.

When considering disease-related parameter of epidemic region model, we merely take into account severity, popularity and endemicity. Besides, the disease is assumed to be transmitted through contacts between people, but in fact, there are also other transmitting methods: through mosquitoes and birds etc. To improve the model, we could consider not only humans, but also other groups as the sources of disease transmitting. Last but not least, people are assumed to be become permanently immune once cured, which is true for diseases like Ebola and SARS. But real condition is much more complicated: a person is likely to be infected again even after recovery; there also exists the superinfection in such diseases like the Malaria.

In conclusion, our model leaves much room for improvement.

Non-technical Letter

Currently Ebola is ravaging the Africa land; the death toll is soaring in several countries. Despite the sorrow observing millions of life perishing, fight against Ebola has never ceased. With the endeavor of World Health Organization and nations, vaccine and medicine for Ebola are successfully developed, and will soon be

manufactured on a large scale. It is hopeful that in the short future nobody will suffer from the violent disease.

To control the disease from further spreading, the medicine will be preferentially provided to epidemic regions where the condition is worse. We take a top-down approach, that is the medicine will be directly air transported to the center of a virus-striken country, then the government is responsible for distributing the medicine. Since in the early period the supply cannot cover the demand, the medicine will be first served to countries where the outbreak is relatively late, so as to maximize the effect of medicine. When the production rate of medicine increases, the medicine will be first served to countries where the number of patients is relatively large, so as to curb the situation.

The vaccine will also go into production recently. We suggest that vaccine be first given to medical clerks and those who are working with animals. Then the rest vaccine are expected to be used in epidemic region with greatest density of patients, protecting susceptible healthy people.

Besides medicine and vaccine, education on Ebola are supposed to be popularized. Small changes in life habits can make great difference. These habits include cutting down travel and reducing exposure in public place. Besides, if those in early period of infection go to hospital in time, not only their lives will be saved but also the probability of Ebola being controlled will remarkably rise.

We sincerely believe that one day nobody will live under the horrible shadow of Ebola. With united efforts the virus will sure be eradicated.

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