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1 Abstract

According to the complexity and uncertainty of situations in the real world, compared to traditional game theory, evolutionary game theory is more applicable to practical problems, such as biological problems or economic issues. Researches on evolutionary game give new ideas to the investigation of complex practical problems.

With the rapid development of science and technology, nowadays diseases is still an important problem threatening human survival. Based on the basic framework of evolutionary game theory, in this paper we survey and study the application of evolutionary game theory in terms of occurrence mechanisms and propagation mechanisms of disease. We analyze the application respectively from two aspects, which are cancer treatment program and controls of epidemic spread by population vaccination. Firstly, in cancer treatment, we mainly analyze evolutionary game results of cancer cells under different treatment regimens and discuss rational application of the "adaptive therapy" in the future cancer therapy. Secondly, in the population vaccination behavior, we analyze issues about dominant population strategy in different factors of operated policy, which was investigated by researchers in different literatures, and discuss the application about evolutionary game theory in the control of epidemic spreading.

Key Words: evolutionary game theory, cancer adaptive therapy, vaccination strategy, G-function, strategy dominance, SIR model.

2 Introduction

2.1 Research background and introduction about evolutionary game theory

Nowadays, people are being tortured by the unprecedented number of diseases, but in the future this situation will continue. It also resulting difficult for us to deal with health issues. Such as the flu crisis, although scientists have struggle with the flu virus for centuries and influenza vaccine technology has very mature, the annual flu season can cause a certain degree of social instability. There is no way to predict that in the future which kind of the specific pathogens will become a health risk. But according to the current disease has occurred, one of the important challenges, which need to be solved by scientists, is that people have able to quickly and efficiently make a control plan and to prevent in advance.

Malignant tumor is one of the major diseases seriously, which threat human health. Cancer, cardiovascular diseases and accidents constitute three major causes of death in the world. As a result, the world health organization (WHO) and health departments in every country's government all list it as a priority that it is imperative to conquer cancer [21]. Cancer known as malignant tumor is harmful to human health, which is caused by a damaged proliferation mechanism of cancerous cells leading to the cells proliferation at an abnormal rate like infinite proliferation and damages other parts of tissues in human body by these abnormal cancerous cells. It is different with the consistent and stable metabolism of normal cells that cancer cells, deriving a result of a related gene mutation, are characterized by a damaged metabolic function which causes the

proliferation in infinite circles with a high rate. Therefore, according to such feature on one hand genes of tumor cells are easily mutable that promotes resistances from anti-cancer drugs, and on the other hand tumor cells easily transfer to other body organs that damages the other function of human body [12].

In the earlier time of conventional cancer therapy like chemotherapy, a main idea of the chemotherapy is an application of a higher dose of single chemotherapy drug, which depends on the limit of the human body tolerance that in order to obtain the largest reduction of cancer cells as much as possible. In the earlier stage of the therapeutic process, the chemotherapy indeed makes a great impact on the population of tumor cells that rapidly kills a large amount of cancer cells. However the chemotherapy also has much deficiencies. On one hand, as the chemotherapy proceeding, the treatment with high dose of anti-cancer drugs can seriously impact on normal cells of the body and at the same time damage other normal cells of human organs, and on the other hand even the dose is high enough it is impossible that cancer cells can be destroyed or eliminated. There indeed exists some surviving cancer cells. Because of the rapid proliferation and the mutation of cancer cells, these surviving cancer cells with prominent evolutionary advantages can enlarge the cancer population again by the heredity of resistances. Ultimately it results in the failure of treatment. Therefore, the most difficult point of the cancer therapy is that in the infinite proliferation the surviving tumor cells can easily obtain the drug resistance with the anti-cancer drugs making tumor cells out of control. Then coming with the impact of tumor cells proliferation which gets out of control, remaining tumor cells grow rapidly in a very short period of time and ultimately form a population of resistances.

Based on such reasons, tumor cells are very difficult to get an effective control from the current therapy. Jessica J. C. and Robert A. Gatenby (2011) [6] present a therapy called "the adaptive therapy" using a simulation model for cancer treatment concerning the evolutionary game theory. General cancer treatments have indeed remarkable effects on cancer cells control while treated on the early stage. Early treatment can make tumor population decline or stabilize as well. However for the malignant tumor cells have strong evolution ability, the traditional cancer treatment could quickly produce adaptability, namely drug resistance. According to the adaption and changes of the tumor in the whole treatment process, the tumor treatment must be administered basing on the evolutionary system of dynamic change. The researches apply a tool of the evolutionary method, namely a fitness generating function (G-function), to predict the ability of the evolution of resistant cancer cells. This function means the response respectively to evolutionary adaptation and micro environmental conditions and response to various therapeutic strategies. With this function, the population change its characteristics over time.

The other investigation in this research is about vaccination behaviors in population. Vaccine inoculation is recognized as an outstanding achievement in biomedical areas and public health areas in the 20th century. Generally as the disease, the preventing method of vaccines is successfully produced. Smallpox was completely eradicated in the world in the past century. Due to the implementation of the planned prophylactic vaccination [19]. It is the same for other diseases, as well as other vaccine can prevent the epidemic and take it under control. However, in terms of disease control, even with related disease vaccine, if the vaccination rate is low, the control of disease will not still be realized.

Therefore vaccination is the key point of the study.

Since vaccination has some risks and costs, people would estimate risks in disease transmission and vaccination. If the risk of vaccination is high or the possibility of disease infection is small, then people do not want to uptake vaccinates. Such laissez-faire attitude will lead to the reappear of disease prevalence. Such attitude in turn influences people to reconsider whether consider the vaccination.

Moreover, in the face of vaccination issues, people usually tend to be in a game dilemma. When some part of people agree to uptake vaccinates, the possibility of infection for unvaccination people is greatly reduced due to all neighbours of unvaccination people are vaccinated. Therefore it is not necessary to participate in vaccination. But if anyone in population decide their behaviours like this, there will not have anyone to uptake vaccinates, in turn the situation accelerates the spread of diseases, which can cause a new round of outbreaks of infectious diseases. There is another aspect in the dilemma. In the case of limited resources, if people fears the presence of the disease, it can cause a situation that people rush to buy and stock a large number of drugs. This situation leads to the price gouging by merchants and then causes more fears and makes the social unrest again. Herd immunity is the most fundamental method to reduce the burden of social health, but on the other hand it will also encourage more people to take "free-rider" behavior [27]. Therefore under the voluntary immunization policy, population vaccination rate will be much lower than the optimal public health vaccination levels. We analyze different approaches applied game theory methods from new perspective such as dynamic, adaptive and self-regulating to explore the structural characteristics

of the population and how does the limited rationality of individuals impact an individual's immune behavior.

Then the investigations by Chris Bauch and Feng Fu discusses the underlying mechanisms about switching population immunization rates from a low level of "Nash equilibrium" to global optimization state in the theoretical level state. According to this research they applied a method, which is a new immune method to prevent the spreading of diseases based on evolutionary game theory. It also explores mutual coupling and co-evolution of the spread of infectious diseases and immunity behavior from a new angle. Meanwhile it studies a physical phenomena and laws, which are reflected in the true complexity of the system, to help people to understand movement patterns in a complex system and provides a theoretical reference for measuring policy issues about the prevention and the control of infectious diseases and provides a better way of how does vaccines distribute in a real social system [8].

Evolutionary game theory is a new application and a different area with game theory, which is a combination of analysis of game theory and the dynamic process of evolution [20]. It is obviously that they are different at the first glance. The classical game theory often emphasizes one kind of the static equilibrium or the comparative static equilibrium for the related participants in game [15]. But in the real world, most of the real game processes for the participants usually are the dynamic processes, that is to say, such kind of game is a game with a long process. During the long process, the participants will change and also the game purpose will change, and these changes will result in the change of the game system, so as to affect the game. According to these dynamic changes in game, the evolutionary game theory conforms more to the objective real world

than the game theory. Therefore it is becoming an important method that using evolutionary game method to study the dynamic development of the practical problems [3][19]. We can use such method to solve problems in many diseases and find an optimal application for this area.

Evolutionary game theory comes from Darwin's theory of biological evolution [11]. In fact, the earlier idea of evolutionary game could be traced back to the interpretation of the concept of equilibrium by John Nash. Nash proposed in his doctoral thesis that the concept of the equilibrium exist two kinds of explanation: one is the interpretation of the rationalism, another is "the mass action interpretation" (Nash, 1950) [10]. The former one of the interpretation comes from the classic game theory, and another one in fact is the way of the interpretation from the evolutionary game theory. Nash said that the realization of the equilibrium did not have to assume that all of the participants had the knowledge of the game structure. The ability to reason a complex process. He assumed that the participants could accumulate the related experience and information through various kinds of pure strategies with the comparative advantages in the decision-making (for example, learning a strategy with gains high). After a period of strategy adjustment, it also could reach to equilibrium. Nash also expounded the basic analysis of the structure of "mass action". Firstly, assuming that each participant took a pure strategy in game, the individuals of the common pure strategy treated as a group, and all the groups made up a larger population. Next, he assumed that every participate in the game was randomly selected from the general population. Then, he assumed that the frequency of strategies with a higher payoff in the population could increase, on the contrary, the frequency of strategies with a lower payoff in the

population could reduce. Finally, on the basis of these assumptions, a frequency distribution of the pure strategy equilibrium could be worked out (sometimes also seemed as the mixed strategy equilibrium). Therefore, although Nash did not clearly put forward the term of "the evolutionary game theory", the thought of "mass action" by Nash actually covered the connotation of the evolutionary game. As the evolutionary game theory are closer to the reality, it is widely used in biology, sociology, economics and other fields.

Besides investigating the evolutionary process, the evolutionary game also attaches great importance to the analysis of the equilibrium, and usually the purpose of the investigation of the evolutionary process is going to find the equilibrium. Due to the replication dynamic is nonlinear, it is difficult to work out the unique solution. Therefore, the purpose of the evolutionary game switches from solving the equilibrium to take an analysis on the stability of the equilibrium. The basic concept of the theory is Evolutionarily Stable Strategy (ESS). The evolutionary stable strategy was proposed by Maynard Smith and Price (1973) [9][4]. The core idea is that, if an existing strategy is an evolutionary stable strategy, there must be a positive invasion of the obstacle, which making sure the existing strategy obtain a higher payoff than the payoff of the mutation strategy when the frequency of the mutation strategy is lower than this obstacle.

2.2 Main contents and section arrangement

This paper mainly includes two sections. The first section describes the effective treatments for cancer research and analyzes different cancer therapies and results, which are proposed in the literature. The results show that compared with single drug model namely monotherapy similar to that of tradition

cancer treatments, many drugs for cancer therapy namely multidrug therapy of cancer cell population density control is more effective, that can keep the population of cancer cells to a very low level. These methods can help analyze and research the combined drug therapy by scientists in the future. The second section analyzes in the complex social network the relationship between individual vaccination behavior and populations vaccination level, and the relationship between vaccination level and scope of an epidemic. The conclusions of literature provide a basis for specifying the vaccine policy. For different social groups there should have different vaccination programs. In this way it can guarantee the effectiveness of the vaccine for the entire population.

3 Investigation about cancer therapy

According to drawbacks of standard tumor therapies such as chemotherapy and radiotherapy where cancer cells usually easily obtain drug resistances, Jessica J. Cunningham, Robert A. Gatenby and Joel S. Brown. investigate a new cancer therapy named "adaptive therapy" in "evolutionary dynamics in cancer therapy" [6] by using a certain dose of an anti-cancer drug, which ensures the drug concentration holding on a reasonable level in an internal environment, which is determined by simulating a develop model of cancer cells through the application of proliferation model of cancer cells, which is constructed by a function called G-function, to inhibit the proliferation of cancer cells and to reduce the tumor size. The "adaptive therapy" is a sustainable treatment, so as to control the overall number level of cancer cells keep in a small range. Such "adaptive therapy" can not only control the development of malignant tumor on the maximum but also reduce the harm of other normal cells in human body as

low as possible because of anti-cancer drugs, which is controlled in a reasonable range determined by the model. According to related population parameters of tumor cells are different in different therapies, the model of tumor cells with the evolution of the tumor cells adaption and under the micro environment in proliferation processes of tumor cells is constructed by G-function. On the basis of such model, authors tested a multidrug therapy, which applied two different treatments in such program and proved that the multidrug therapy was a more effective therapy with evolutionary strategies than the monotherapy, which was based on a single medicine. Analyzing the process, we get a result that an important point of such multidrug therapy is selecting a right time point for using the second drug, at which tumor cells become vulnerable to the second drug that not quickly produces resistances to the second drug due. The effectiveness of the resistance reduction of tumor cells to the second drug depends on the impact of a drug in the first treatment. A point of the second drug takes advantage of the vulnerability of tumor cells for different types of drugs. Only in this way resistances of tumor cells can be reduced by the different treatments. Such process of the multidrug therapy is an optimal approach, which can control resistance effects of cancer cells by therapies which are produced by the current process of therapies and continually and effectively inhibit the proliferations of cancer cells. That would change how we approach medicine.

Jessica J. Cunningham, Robert A. Gatenby, and Joel S. Brown (2011) [6] applied G-function to construct a basic model. The exact mathematical model are useful to simulate the efficiency of cancer therapy and the realization of cancer therapy. G-function is applied to most biological situations describing the fitness of a population (here is constructed by Darwinian Theory) [14]. For

a biological population, overall individuals in a population have a same strategy set, which includes different strategies selected by these individuals in the population. The fitness of each individual is defined by G-function and an evolutionary game theory. Different with the traditional game theory, evolutionary experiences consider not only one individual but a population and that behaviors of all individuals cannot depend on a rational thought. With evolutionary game theory we can describe a dynamic process how the density of population changes over time under some evolutionary behaviors. Therefore the model could be applied to simulate the population change of tumor cells over time under some evolutionary resistances.

3.1 Description of methods

The two basic ideas of evolutionary game theory are the evolution theory in Darwinian Theory and Lamarckisms biological genetic theory [14]. In an evolution process, only a group with a higher payoff (reproductive survival rate) can survive from competitions, and in opposite a lower payoff group can be eliminated from competitions. This process is namely called "evolution". According to analysis of biological evolution, behaviors of plants and animals are considered as an instinct of an intuition without thinking. Basing on the principle of the evolution, for a population behaviors of individuals finally can tend to Nash equilibrium. The combination of evolution theory and game theory gives a possibility to explain the impact of individuals' behaviors in the process of human groups or any biological groups. According to researches of all behaviors of participants in a group of evolutionary game, the unique condition that regardless of the demand for rational can make it more close to the

biological activity of reality [8]. Nash equilibrium (NS) is a definition of game theory. It is an optimal strategy called Nash equilibrium if and only if a payoff of a NS strategy is not less than other strategies in game. To the evolutionary game theory, a similar concept of Nash equilibrium is evolutionary stable [3].

The first definition of evolutionarily stable strategy (ESS) was given by Maynard Smith(1974) [15]: ESS is a strategy such that, if all members of a population adopt it, then no mutant strategy could invade the population under the influence of natural selection.

Definition 1. We say that x is an *evolutionarily stable strategy* (ESS) if for all $y \neq x$, there exists some $\bar{\epsilon} \in (0, 1)$, which may depend on y, such that for all $\epsilon \in (0, \bar{\epsilon})$

$$u(x, \epsilon y + (1 - \epsilon)x) > u(y, \epsilon y + (1 - \epsilon)x). \tag{1}$$

That is, x is ESS if, after mutation, non-mutants are more successful than mutants, in that case mutants cannot invade the system and will eventually get extinct. We refer to $\bar{\epsilon}$ as the *invasion barrier*, the maximum rate of mutants, against which x is resistant.

G-function can be constructed by three steps. The first step is to select an appropriate ecological model for current population dynamics. The model may be taken for a single population or species. It may be a life-history model with different age and stage classes, or it may be a model of population interactions that includes growth equations for competitors, resources, predators, etc. The second step is to set strategies and strategy sets associated with the population, species or communities under consideration. The strategy set may be continuous or discrete and determined from hypotheses concerning genetic,

developmental, physiological and physical constraints on the set of evolutionarily feasible strategies. The third step is create the G-function by hypothesizing how the individuals strategy, v, as well as all strategies in the population, u, influences the values of parameters in the ecological models of population dynamics. As soon as key parameters of a population model become functions of $v, \mathbf{u}, \mathbf{x}, y$, the ecological model becomes a G-function [14].

Definition 2. (G-function)A function $G(v, \mathbf{u}, \mathbf{x})$ is a fitness generating function (G-function) for the population dynamics if and only if

$$G(v, \mathbf{u}, \mathbf{x})|_{v=u_i} = H_i(\mathbf{u}, \mathbf{x}), i = 1, ..., n_s. \tag{2}$$

Where $\mathbf{u}$ and $\mathbf{x}$ in G are exactly the same vectors as in H_i. The population has n_s different species. The population size is $\mathbf{x} = [x_1, ..., x_{n_s}]$. This is the G-function for the simplest problem with scalar strategies [14].

The fitness generating function $G(v, \mathbf{u}, \mathbf{x})$ eq. 2 determines the expected fitness of an individual using a strategy v as a function of its biotic environment that includes the extant strategies found among the different species within the population $\mathbf{u} = [u_1, ..., u_{n_s}]$, and the different population sizes x_i, $\mathbf{x} = [x_1, ..., x_{n_s}]$. Because there are n_s different strategies, it is reasonable to assume that the fitness of individual i is the sum of the expected payoffs of playing u_i against all strategies in proportion to their numbers in the population.

In the article, authors applied a G-function like this [6]:

$$G(v, u, x) = r\frac{K(v) - \sum_i x}{K(v)} - \mu(v). \tag{3}$$

To tumor cells, a real meaning of the fitness relates to the per capita growth rate. For vectors u, v, they present all phenotypic strategies currently of each tumor cells. x is the population size of those cells. The cells growth rate r is the nature rate without limitations like other affections. The carrying capacity of the tumor cell in population, K, references its ability to survive. And μ is the cell mortality or the suppression hold in a current treatment.

In reality it is possible to treat a cancer treatment process as an ecological game process. Therefore tumor cells are treated as a predator and the treatment is treated as a preying one. It describes a behavior among one tumor cell and other tumor cells. When two cells select different strategies, they would produce a different growth suppression between them because of competitions in resources and space. As to different groups of population, different strategies of cells will lead to different per capita growth rate.

Therefore the fitness function of one tumor cell is determined by G-function with its focal strategy v and other tumor cells' strategies $u \in \mathbf{u}$ and the population size of tumor cells x. For a group which selects the strategy u_i with the population proportion of the current group x_i, the evolutionary dynamic including the population dynamics and the strategy dynamics can get from G-function:

$$\frac{\partial x_i}{\partial t} = x_i G|_{v=u_i}. \tag{4}$$

$$\frac{\partial u_i}{\partial t} = S\frac{\partial G}{\partial v}|_{v=u_i}. \tag{5}$$

x_i represents the proportion of those cells which selects the strategy $v = u_i$ in the total population of the evolutionary system $x_i \in \mathbf{x} = [x_1, ..., x_2]; v = u_i \in \mathbf{u} = [u_1, ..., u_i]$. The focal cell with its own resistance strategy $v = u_i$ is determined by other cells. In eq. 4 and eq. 5, $\frac{\partial x_i}{\partial t}$ presents the population dynamics with time t; $\frac{\partial u_i}{\partial t}$ presents the strategy dynamics and shows the resistance trend of tumor cells with time t. Here S scales the speed of evolutionary change. In evolutionary dynamics a key factor of adaptation to any therapies is the phenotypic cost of resistance. This gives a model of how does tumor cell adjust to a population suppressing treatment [14]. It obviously obtains the change of tumor cells' adaptation from these functions.

$$\frac{\partial x}{\partial t} = rx(\frac{K - x}{K}) - \mu x. \tag{6}$$

It is applied to measure the population growth rate of tumor cells. Here the tumor cells population density, x, is a way to measure the change of population scope.

In the eq. 6, tumor cells' growth rate r is a given number which is known without limitations like other affections. μ and K are necessary to be measured. The parameter μ is effected by three aspects of ecological predation. The three aspects of ecological predation in tumor cells are respectively the encounter rate of predators (also is chemotherapy dosage attributes), the lethality of predators without vigilance of preys (also is the resistance of tumor cells to a chemotherapy), and resistances offered by preys (also means resistances of tumor cells). Those three aspects make up the tumor cell mortality or suppression.

$$\mu = \frac{m}{k + b_e + b_p v}. \tag{7}$$

Here m is the number of the dose of the anti-cancer medicine in the current therapy. And k is the mean of the phenotypic resistance without considering any factors. b_e represents the resistance from environmental factors. b_p is the mean of the effectiveness of resistances, which act as promotion strategies. v is the effectiveness of evolutionary strategies. Therefore $b_p \cdot v$ indicates the impact of evolutionary behaviors. Integrating the mortality or the suppression of tumor cells with all relevant parameters eq. 7, μ indicates the effectiveness of drugs and also the resistance of tumor cells.

The carrying capacity of cells K is relative to:

$$K = K_{\max} \exp(\frac{-v^2}{2\sigma_K^2}). \tag{8}$$

The parameter K represents the cost of resistances through the population carrying capacity. And v is the mean of resistance strategy. And b_K represents the resistance penalty of tumor cells. In a prior process, without any treatments $v = 0$, therefore $K = K_{\max}$. Over the time of treatment, v will increase and K will decrease. σ_K^2 is the resistance penalty of tumor cells, which is related to the range of resources. A small value of σ_K^2 means lacking resistances and results in a large penalty.

3.2 Analysis of applications about cancer therapies

In this article authors apply the tool of G-function to three basic therapies. They are monotherapy, multidrug regimens with one response and multidrug regimens with two responses. The monotherapy is a treatment with a single drug. The multidrug regimen is a treatment with two process of taking same or different drugs.

3.2.1 Simulation about three basic regimens of cancer therapies

According to different responses to drugs, authors simulate three regimens respectively by a single response with a single drug, different responses with one drugs (different doses with different drugs) and two different responses with two different drugs.

With same parameters like a same tumor size and same characteristics of the common group of tumor cells, these parameters set as follows: a constant size of tumor cells $x = 100$, a constant carrying capacity $K_{\max} = 100$, a constant normal tumor cells growth rate $r = 0.1$, the resistance penalty of tumor cells $\sigma_K^2 = 5$, a constant effectiveness of the resistance $b_p = 5$, the phenotypic resistance without considering any factors $k = 0.1$ and without the resistance from environmental factors $b_e = 0$. In order to get different responses to one drug, this process settles the single drug with different dosages $m_1 = 0.1$ and $m_2 = 0.12$ by increasing drug regimens.

In order to test a multidrug therapy, G-function can change the form of different dose of drugs applied by eq. 6, eq. 7 and eq. 8.

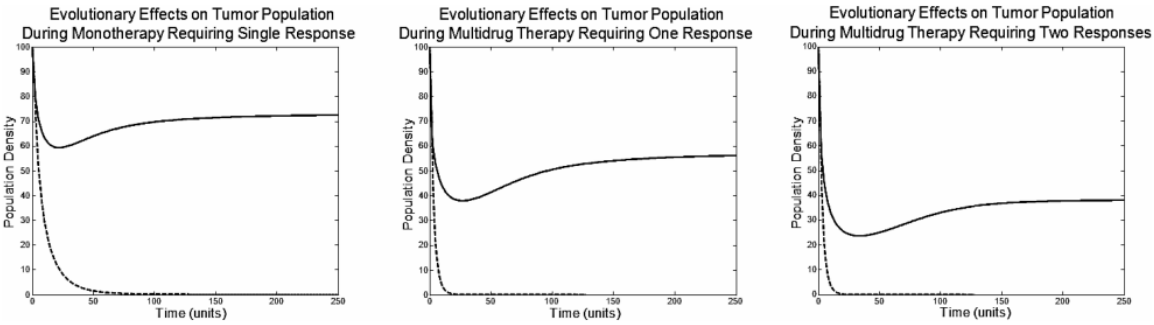

Figure 1: Comparison about evolutionary effects on tumor population.

$$G(v, u.x) = r\left(\frac{K(v) - \sum_i x}{K(v)}\right) - \mu_1(v_1) - \mu_2(v_2). \tag{9}$$

The trend in fig. 1 shows results of three basic experiments. The vertical axis indicates tumor population density with three different basic treatments. The full line represents the population trend with evolutionary abilities. The dotted line represents the population trend without evolutionary abilities. From the dotted curve, the population density are obviously drop to zero in a very short time unit. Differently, processes about the multidrug therapy respectively with one response and two responses all make the population density curve more strictly drop than the treatment process with the monotherapy requiring one single response. Firstly, let us consider cases with evolutionary abilities. In monotherapy requiring single response with the time point of the curve mostly close to $t = 70$, tumor population drops to $x = 0$. The multidrug therapy requiring both one response and two responses similarly make the tumor cells population decreasing to $x = 0$ in time unit $t = 70$. The result indicates that the multidrug therapy has a better effect on the control on the population density than the monotherapy. Secondly, let us consider cases with evolutionary abilities

as these full lines. These full lines show the results of these treatments processes with the evolutionary ability in phenotypic resistances. Different from the non-evolution process, the lowest points of population density in these treatments with evolution are identically far from zero. It means that these evolutionary abilities advance the survival rate of tumor cells. The population density curve of the treatment process with the monotherapy with single response has a lowest point $x = 60$ at $t = 20$ and finally reaches to a stable state $x = 73$ after 130 units of time. The curve of the treatment process with the multidrug therapy with one response has a lowest point $x = 38$ at $t = 20$ and then finally reaches to a stable state $x = 57$ after 150 units of time. The curve of the treatments with multidrug therapy requiring one response has a lowest point $x = 23$ at $t = 25$ and then finally reaches to a stable state $x = 38$ after 150 units of time. These results indicate that effects of the monotherapy is the worst and effects of the multidrug therapy requiring two responses are better than the therapy requiring one response. However all these treatments are not yet able to eradicate the tumor population density.

According to graphs above, the multidrug therapy requiring two responses has most high reduction on tumor population density. Under the situation that tumor cells have evolutionary abilities, the population density will increase over time. Therefore authors view a further model. Different with the previous model, the frequency of taking drugs in the model is taking drugs at $t = 0$ and then off at $t = 50$. The cycle of the process is $t = 100$. The treatment cycle is used to check how resistances of tumor cells impact the population density of tumor cells.

Top axis: the fractional resistance, v_i, to the one or two treatments given

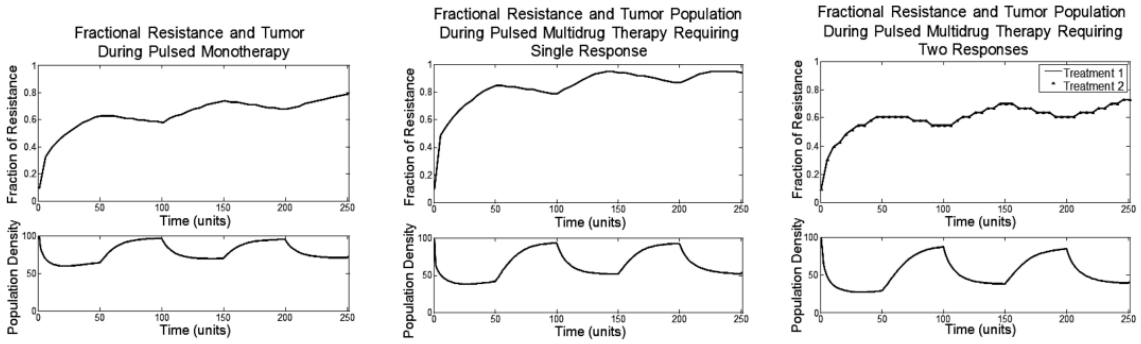

Figure 2: Evolutionary effects on tumor population with time units.

over time; bottom axis: the population density of the tumor. The time axis means periods of treatment (50 time units) that alternate with periods of no treatment (50 time units). It means treating for 50 time units and abandoning for 50 time units.

In the top axis, it shows that the fractional resistance v of tumor cells to different treatments has a progressive increase over time. The bottom axis shows the population density of the tumor cells. Initially all these treatments create obvious reduction in the population density of tumor cells, but the value of the reduction drops during the first 50 time in one cycle $t = 100$ according to the developing resistances of tumor cells. The monotherapy requiring single response makes the population density drop to $x = 58$ at the first 50 time units. Without using drugs in the next relaxation period the population density curve has a quick recovery closing to $x = 99$ at the end of the cycle $t = 100$. The curve of treatments in the multidrug therapy requiring one response drops to a stable state $x = 43$ at $t = 20$ until the end of the first 50 units of time. In the next time interval the curve about lacking drugs has a quick increasing from $x = 43$ to $x = 98$. Therefore in a 100 time interval the treatment causes results that

the tumor population recover to $x = 98$. To the multidrug therapy requiring two responses the population density in a treatment course drops $x = 30$ and maintains a stable state during the 50 time interval. In a next 50 time interval the curve without drugs quickly recovers to $x = 85$.

From different curves in fig. 2, the trend curve of treatment processes in the multidrug therapy requiring single response is higher than treatment courses in the monotherapy. It indicates that the treatment process with a high dose of drugs is completely ineffective to tumor cells. During each treatment cycle, the population size is decreasing under the treatment and recovers without any treatments applied. On the other hand, evolutionary resistance abilities of tumor cells are directing towards increasing. With enough cycles, tumor resistances will become completely overall. Therefore there is no effective result in taking about eradicating tumor cells.

3.2.2 Evolutionary double-bind therapy

In this article [6], authors putted forward a more strategic therapy. Evolutionary strategy theory shows that predators usually obtain adaptabilities for certain prey behaviors by the preys during the evolution process. But in most cases this evolutionary process will hinder the obtaining to the adaptability of preys by different feeding behaviors with other predators. From another point of the view, different behaviors of different predators would making the feeding behavior to be more effective through weakening prey adaptabilities. Concerning the interrelation between different drugs therapies and cancer cells, it is a kind of a therapy that the implement of one treatment can reduce resistances of cancer cells to other different treatments. According to this feature, authors

design one therapy that two different treatments alternatingly switch the administration by a periodic way. Under the first stage that applies one treatment it is realized that cancer cells are killed mostly and at the same time the treatment drives cells to obtain an evolutionary response, making the effect of cancer cells' resistances to the second treatment attenuating. It is benefit for the second stage that using the second treatment with a better effect, and at the same time weakening cancer cells' resistances to the first treatment, which produces in the first stage.

According to this scheme, there is new examination with the model by authors. The main idea of the part is "predator facilitation". These processes in the double bind therapy includes two parts, in which weak cells will be easily attacked once the second drug is applied. It is said that the evolutionary one will be targeted by the second therapy. Different with the previous parameter μ, here authors set μ_1 and μ_2 presenting the proliferation suppressions by different treatments which used in each process.

$$\mu_1 = \frac{m_1}{k_1 + (1 - v_2)(b_{p1} v_1)}, \tag{10}$$

$$\mu_2 = \frac{m_2}{k_2 + (1 - v_1)(b_{p2} v_2)}. \tag{11}$$

Here m_1 and m_2 are different doses of drugs in each treatment. v_1 is tumor cells' evolutionary strategy by m_1 drug, and v_2 is tumor cells' evolutionary strategy by m_2 drug. b_{p1} and b_{p1} represent the effectiveness of resistances with the first and the second treatment. And G-function could be written as a new

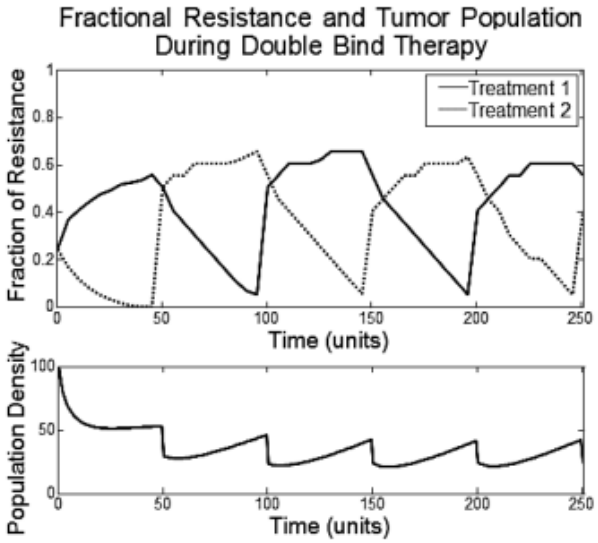

Figure 3: Double bind therapy.

expression:

$$G(v,u,x) = r\left(\frac{K(v) - \sum_i x}{K(v)}\right) - \mu_1(v_1) - \mu_2(v_2). \tag{12}$$

The top axis represents the fractional resistance v_i in the double bind therapy over time; bottom axis represents the population density of the tumor over time.

In fig. 3 the curve shows the fraction of resistance and the population density by the new function. From curves above, in the double-bind therapy when using the first treatment the fraction resistance of cancer cells for the first treatment are increasing from the initial value $v_{t=0}$ during the first treatment process. In the meantime the fraction resistance of cancer cells for the second treatment is decreasing as the first treatment process going. At the right point in time (here authors set 50 time interval in one treatment process), the multidrug

therapy switches to the second treatment. In the second process the efficacy of the second treatment becomes more effective, and at the same time phenotypic resistances of cancer cells to the second treatments are increasing rapidly, but phenotypic resistances of cancer cells for the first treatment are consequently reducing over time. But the population density of cancer cells during the treatment has a trend of declining. Even after a period of time with application of the double-bind therapy, the population density of cancer cells would be a low population density stable within a certain range and not continually decrease any more. But cancer cells will continually have resistances in switching two kinds of evolution reactions, until resources exhaustion.

Authors gave an experiment on a recently research about a new therapy with p53 cancer vaccine combined with chemotherapy. To a certain extent, it also supports the validity of the double-bind therapy. The p53 vaccine is one kind of cancer vaccine. The vaccine could stimulate the body's immune response. On one hand, the immune response could suppress tumor cells, and on the other hand, such response is a degree of resulting cancer cells to become vulnerable. In this research, it discussed the immunological research and the clinical effect about the combination therapy with p53 cancer vaccines for lung cancer patients. According to the immunological research data, p53 cancer vaccine has no significant clinical response for controlling the population of cancer cells.

Top axis: the fractional resistance v_i to the two treatments given over time; bottom axis: the population density of the tumor.

It is visible to see from the fig. 4 that in the p53 vaccine stage it does not produced a significant response but promoting the effect of the following

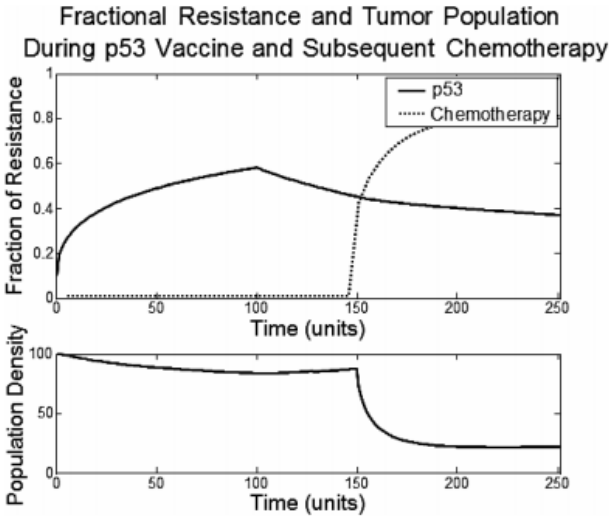

Figure 4: p53 vaccine and subsequent chemotherapy.

chemotherapy. The fraction of resistance in p53 vaccine is increasing after taken. In the curve of population density, there drops less than 15 during the vaccine treatment. It indicates that the vaccine has a very small effect to the population density. The methods for application is choosing a right point in time. The vaccine process stops at $t = 100$ and the chemotherapy treatment is applied at $t = 150$. The subsequent process of the chemotherapy treatment produces a significant response as the rate of 62%. Compared with the historical data, there have a significantly larger improvement of the chemotherapy rather than the 8% response rate with no p53. From the data of the synchronized blood test there also gets a support. It presents that the better responses to chemotherapy certainly present in the patient who has a better immune response for p53 in the treatment process. In other words, the adaption of tumor cells in the immune therapy drive their evolutionary resistance to become more sensitive to the chemotherapy drugs.

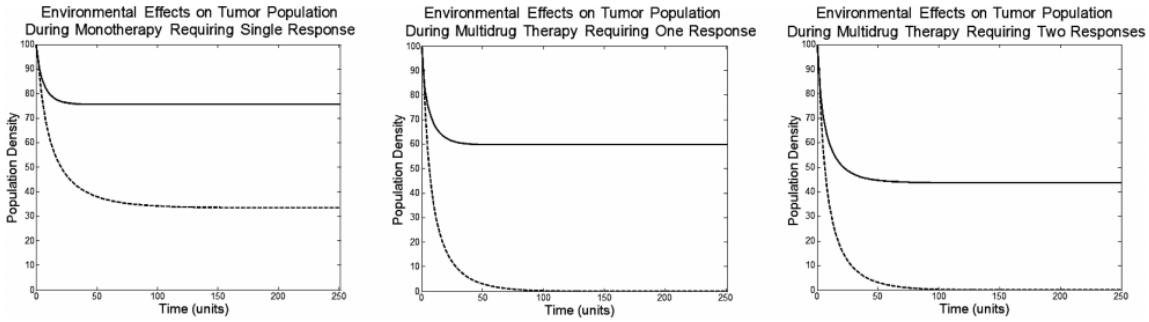

Figure 5: Denovo environmental resistance.

3.2.3 De novo environmental resistance therapy

In the further research, the authors focus on the role of the microenvironment of tumor in the process of driving new resistance. Here microenvironment mainly refers to the tumor vascular structure and the blood flow. There has two aspects of the microenvironment. On the one hand, due to the reduced of the blood flow, it makes the ischemia hypoxia. On the other hand, for drug delivery blocking it influences the drug effect. This factors involves the parameter b_e in the authors model. Keeping the value of parameters except the b_e in the prior model, b_e will be changed from 0 to 1. With using the new coefficient of the environmental resistance, the μ_1 and μ_2 in eq. 10 and eq. 11 would be written in the new formula:

$$\mu_1 = \frac{m_1}{k_1 + b_{e1} + (1 - v_2)(b_{p1} v_1)}, \tag{13}$$

$$\mu_2 = \frac{m_2}{k_2 + b_{e2} + (1 - v_1)(b_{p2} v_2)}. \tag{14}$$

Top axis: the fractional resistance v_i to the two treatments given over time; bottom axis: the population density of the tumor.

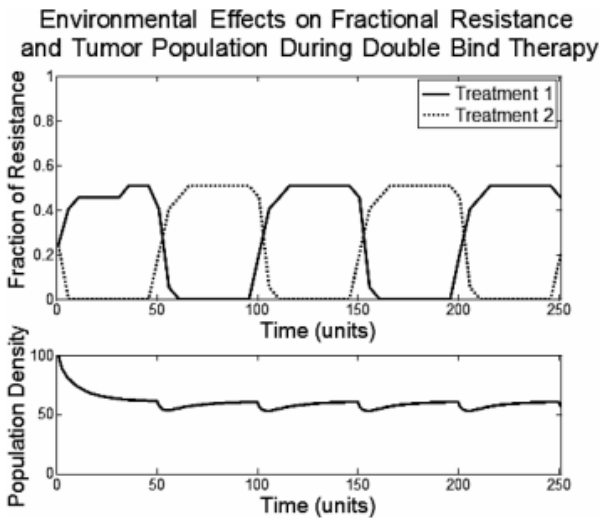

Figure 6: De novo environmental resistance therapy.

The simulation is an application of the previous three basic treatment which is absent of environmental factor. For such application, comparing with no environmental resistance of cancer cells (like testicular cancer and lymphoma) in fig. 1, such results with the impact of environment in fig. 5 are closer to the majority of the type of tumor. With small doses of the drug treatment, cancer cells are more likely to have serious drug resistances.

The curve in fig. 6 shows there has 44% reduction in cancer population density with the de novo environmental therapy. It has 24% increase comparing results of no environmental resistance. The de novo environmental therapy still effectively inhibits the formation of cancer cells resistances and at the same time inhibits the development of cancer cells population, which prevents the tumor regeneration.

3.3 Conclusion

It can be seen from the simulation that this kind of cancer therapy has a good impact of the issue in the traditional single cancer therapy, which can quickly increase cancer cells resistances by high doses of anti-cancer drug, not only inhibits the cancer cell population density but also makes the single drug disabled. It plays an important role in the development of controlling cancer cells population density, effectively inhibits the increase of the tumor and regeneration and avoids the emergence of serious drug resistances. There is no doubt that the "adaptive therapy" comparing with the traditional chemotherapy is more powerful and effective, suitable for more patients and can save more lives.

Results from experiments show that even the "adaptive therapy" makes significant reductions in the cancer cells population density. But only keeping the cancer population density to a lower level, it has not fundamentally solved the problems of eradicating tumor. Moreover, factors influencing environmental resistances in a real case are more complicated than the model. In fact, this therapy could make the cancer cells population density keeping down to a level, which is not ideal, due to the influence of environment resistances. With the passage of time, resistances of cancer cells during the evolution process will develop to a serious degree, the therapy leads to cancer cells population density expanding with no limit, finally making a failure.

From the conclusion of "adaptive therapy" [6], it can clearly show that there has a stationary phase for the tumor population during the simulation process of the cancer therapy. It is an advantaged way for follow-up treatment. If making good use of this section, it may receive an unexpected effect. Also it can be found that the cancer cells population density has a downward trend in the

time interval which has a selection in the first stage of switching two treatments. Then it may foresee that, if three treatments, or more alternative treatments could apply to a therapy, the cancer cells population density is possible to reduce to a lower level and avoids continuing develop towards a high level. An approach of the "adaptive therapy" can also be changed flexibly to achieve better treatment effects according to the current status of the cancer cells population density.

4 Investigation about the impact of population vaccination behaviors

Vaccination is recognized as one of the best strategy for the prevention of diseases in the world, and has developed for more than 200 years, with benefits that vaccinates has already completely eradicated many infectious diseases, which had a serious threat to human health during past years and had been disappeared from public view. In a vaccination situation report published by World Health Organization (WHO) in 2009 [7], it showed a status report about the global alliance for vaccines and immunization status. The report pointed out that immunization, as a core power, played a vital role in disease control in order to reduce the mortality of new born children under the age of five. More and more children have accepted vaccinations. From 2005 to 2007, more than one hundred million children have uptake the vaccine each year. Many lives are saved.

4.1 The strategy of children diseases intentions vaccination

Although children vaccinations obtain great achievements, there still have some children without finishing the degree of immune regulations. After some emergences of bad cases about vaccines, people consider that it must be doubtful that whether should necessarily take vaccinations. According to lacking popularization of information, a growing number of unsafe factors of vaccines causes a narrow popularity of vaccinations. However, the reduction of the vaccination level possibly leads to many diseases reappear, which has already become extinct. Some bad realities have shown the situation in history. Although prob-

lems of vaccines do exist, it is no doubt that the application of vaccines indeed makes it realize that control and extinct many diseases. Vaccine absolutely is the most cost-effective way for preventing diseases. In ""vaccination of the found of games" (2004) [19] Chris Bauch written, there is a new model, which combined a game theory framework with epidemic model for predicting vaccination behaviors of individuals and describing how parents decisions of their children vaccinations, which are influenced by a judgement of risk perceptions about vaccinations. And their vaccination behaviors will affect the expected coverage level of vaccination.

In game theory, decision-making behaviors appears in occasions that two or more individuals interact, the decision of each individual depends on the prediction of this individual as for other individual behaviors. By selecting the best decision-making behavior, the aim is to seek profit or utility maximization.

4.1.1 Description of mathematical models

In game theory, the selection of different strategies appears in such occasions that two or more individuals interact, and a decision of each individual depends on the prediction of this individual as for other individual behaviors. For selecting the most optimal strategy, the aiming point is to seek profit or utility maximization.

In the prediction for vaccination and vaccine coverage level, the behavior of each individual in the group has a decisive influence on the result of population. There are two mainly aspects of factors influencing choices of individuals vaccinations whether it is necessary in population. One aspect is the risk of the vaccination behavior itself. Another aspect is the infection risk of disease

related the vaccine. In order to make a prediction, it is necessary to build mathematical models and analyze them. For simplifying such process, authors assume that all individuals should receive the same information and evaluate and handle information by the same way.

Firstly for analysis of individuals perceptive risks of vaccines, authors mainly mentioned perceptive risks, which brought by safety issues of vaccines. Because of some vaccines are made from deactivated versions of viruses, it also has a very small possibility of becoming pathogenic for unfortunately technological mistakes or artificial defects [6]. Actually mostly vaccines are fairly safe. However some opposite events relating to dangers of vaccines occurred in the past. Even these cases was confirmed false. Public mistakenly thought that such events revealed many problems of vaccines. It leaded to increase the perceptive risks of the public and leaded that people missed the best time to vaccinate. Further these events affected the overall coverage level of vaccinations. According to the vaccinate risk factor, authors applied the parameter r_v to define the risk of vaccine.

Secondly, according to analysis of the infection rate of diseases, authors mainly mentioned an infection rate, which brings by the disease and besides under the uptake level of a population impacting individuals' choices of vaccination behaviors. With the information, on one hand that vaccines could prevent infecting diseases, individuals should have higher probabilities to choose vaccination, and on the other hand, if the diseases cannot be prevented spreading to serious consequences by vaccination, individuals should have higher probabilities to reject vaccination. When the vaccination level in population reaches to a certain level, vaccines will certainly prevent the spread of diseases in a crowd.

According to these disease related factors, authors applied r_i to represent the risk of the infection diseases and π_p to represent the probability of the infection disease in unvaccinated individuals under the vaccination level of p.

In game theory, when decision-making strategies by two or more individuals occur by interactions between, each individual decision depends on the prediction of behaviors of other individuals. By selecting the best strategy, it could be realized that the payoff of individuals or groups could get maximize [19]. For a vaccination strategy, the expected payoff should be calculated as follows:

$$E(P, p) = P(-r_v) + (1 - P)(-r_i\pi_p). \tag{15}$$

The first part in the right side of the equal sign is the expected payoff of the vaccinated individual with the probability P under perceptive risks of vaccinations and the vaccination level of p. The second part in the right side of the equal sign is the expected payoff of the unvaccinated individual with the probability $(1 - P)$ under risks of diseases and the vaccination level of p. In this function eq. 15 the morbidity risks from vaccination r_v and infection rate r_i could simplified by the relative risk $r = r_v/r_i$ instead of different types of risk parameters, then they get a new payoff function,

$$E(P, p) = -rP - \pi_p(1 - P). \tag{16}$$

In the paper, while adding factors of vaccination to the susceptible-infected-resistant model (SIR model), or epidemiological model. The first definition of

SIR model is presented by Kermack and McKendrick (1927) [13]. Authors analyzed the transformation law of the different groups in population under the action of vaccines. SIR epidemic model is constructed in accordance with the general transmission mechanism. In the general transformation mechanism, the population is divided into different parts, and each part could mutually transform step by step. Such model describes the spreading process of infectious disease, analyses the changing rule of infections, and reveals the development trend of infectious diseases through the quantitative relation of infectious diseases.

The SIR model is also called "three-component model". S is the mean of susceptible people. I is the mean of infective people. R is the mean of removed people. The scope of the population of the epidemic model is divided into three categories: S part (Susceptible) is uninfected individuals but lacking the immune ability, after contacting with the infected person turned to infection; I part (Infective) is infected individuals, and it could influence S part; R part (Removal) refers to isolated individuals, and another part of individuals, which obtain immunity after illness. Three parts could transform by the way as $S \rightarrow I \rightarrow R$.

In such model, suppose that individuals with uptaking vaccines will not be infected any more, therefore: Susceptible part equals unvaccinated individuals of new born population in unit time minuses healthy people becoming infected in unit time and then minuses healthy people eventually natural death in unit time. Infective part equals healthy people becoming infected in unit time minuses cured patients in unit time and then minuses healthy people eventually natural death in unit time. Removal part equals vaccinated individuals of new born population with the permanent immunity in unit time pluses cured patients

in unit time and then minuses healthy people eventually natural death in unit time.

Such model could be expressed as follows:

$$\begin{aligned} \frac{dS}{dt} &= \mu(1-p) - \beta SI - \mu S, \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I, \\ \frac{dR}{dt} &= \mu p + \gamma I - \mu R, \\ S + I + R &= 1. \end{aligned} \tag{17}$$

Here, μ is the mean birth and death rate of population, $\mu(1-p)$ is unvaccinated individuals, β is the mean transmission rate of diseases, γ is the mean cure rate of diseases, and p is the vaccine uptake level.

$$\begin{aligned} \frac{dS}{d\tau} &= f(1-p) - R_0(1+f)SI - fS, \\ \frac{dI}{d\tau} &= R_0(1+f)SI - (1+f)I. \end{aligned} \tag{18}$$

The parameters in this function $\tau = t/\gamma$ are time measured in units of the mean infectious period. $f = \mu/\gamma$ is the infectious period as a fraction of mean lifetime, and $R_0 = \beta/(\gamma + \mu)$ is the basic reproductive ratio. The basic reproductive ratio presents that an infected individual causes new infections during a unit time period.

Herd immunity is a method of controlling the spread of infectious diseases. It means when the level of the vaccination reaches to a range, the overall population will not infected any more. This method could reduce S_0 through vaccination. That is to say, through the herd immunity it could be realized that the spread of infectious diseases is stopped by the initial susceptible persons all immune.

So the critical coverage level that eliminating the disease could obtain from the SIR model.

$$p_{crit} = \begin{cases} 0, & \text{if } R_0 \leq 1, \\ 1 - \frac{1}{R_0}, & \text{if } R_0 > 1. \end{cases} \tag{19}$$

When $p > p_{crit}$, $S = 1 - p, I = 0$, this situation means that with the vaccine uptake level p reaching to the threshold. Under this threshold level overall population will be immunity and population outbreaks will not happen. Thus nobody else gets sick in this situation. When $p < p_{crit}$, it means that the vaccine uptake level p is smaller than the level of disease eradication, then some people must be infected. Thus the vaccine uptake level p should be stable coverage to the threshold. The SIR system could converge to a stable endemic state as follows:

$$\begin{aligned} \hat{S} =& 1 - p_{crit}, \\ \hat{I} =& \frac{f}{1+f}(p_{crit} - p). \end{aligned} \tag{20}$$

Here is a problem of the convergent stability. Before explaining the convergent stability, let us introduce the application of Nash Equilibrium applied in the article.

4.1.2 Nash Equilibrium in the prevention of diseases

Definition 3. (Nash Equilibrium): The Nash equilibrium is a collective strategy in a game involving two or more players, where no player has anything to gain by changing only their own strategy. Formally, a set of two strategies played by

players A and B (p_A, p_B) is a Nash equilibrium if

$$\begin{aligned} E_A(p_A, p_B) \geq & E_A(q_A, p_B), \ for\ all\ q_A, \\ E_B(p_A, p_B) \geq & E_B(q_A, p_B), \ for\ all\ q_B; \end{aligned} \tag{21}$$

Where q_A and q_B describe any other strategy that can be played by players A and B respectively, and E_A and E_B are the players payoffs. The p_A and p_B to mean a particular strategy like cooperate or defect in the prisoners dilemma (these are called pure strategies). But games can also be played with a random element, where p_A and p_B are the probability distributions for all the pure strategies a player can play (these are called mixed strategies). In the case of mixed strategies, E_A and E_B is the expected payoff obtained from random encounters between mixed strategy p_A and p_B.

As a stable and dominant state, the Nash equilibrium is able to give a judgment strategy to determine the optimal strategy for the group. For the real case, the Nash equilibrium is the strategy with a better payoff. If the majority of individuals selection is strategy P, individuals with strategy Q always obtain the lower payoff comparing with the mostly individuals choosing P. Then the strategy P is called a Nash equilibrium. If P is a Nash equilibrium and currently each individuals choose P, there is no one will change own strategy. In the population strategy P has be chosen by proportion ratio of the population for epsilon, and strategy Q with ratio of $(1-\varepsilon)$. Then the ratio of entire population strategy, namely:

$$p = \varepsilon P + (1 - \varepsilon)Q, \tag{22}$$

With the payoff gain we could measure the incentive of individuals which switching strategy in Q and P,

$$\Delta E = E_P - E_Q = (\pi_{\varepsilon P+(1-\varepsilon)Q} - r)(P - Q), \tag{23}$$

When $\Delta E > 0$, the strategy P is the dominant of those strategies and will be chosen. Where Q is the dominant strategy.

Payoff functions can be constructed respectively for P individuals and Q individuals,

$$\begin{aligned} E_P(P, Q, \varepsilon) =& E\big(P, \varepsilon P + (1-\varepsilon)Q\big), \\ E_Q(P, Q, \varepsilon) =& E\big(Q, \varepsilon P + (1-\varepsilon)Q\big). \end{aligned} \tag{24}$$

Here authors gave a definition of the convergent stability.

Definition 4. (Convergent Stability): If the majority of individuals same selection is strategy Q and some individuals choose the strategy closer to P than Q, the payoff of the strategy closer P obtains the higher payoff than those who individuals with strategy Q (from P strategy to lower revenues). Under this situation if any $Q \neq P$ is true, then P is known as the convergence and stability.

Then the probability of an unvaccinated individual becoming infected π_p could be expressed with the vaccine uptake level of p:

$$\pi_p = \frac{R_0(1+f)\hat{S}\hat{I}}{R_0(1+f)\hat{S}\hat{I} + f\hat{S}} = 1 - \frac{1}{R_0(1-p)}. \tag{25}$$

Here $\hat{S}$ and $\hat{I}$ represent estimated values of S part and I part. For the real case, when the perception risk of vaccinations is larger than the infection rate of disease $r > \pi_0$, the result of CSNE is rejecting vaccinations $P^* = 0$; when the perception risk of vaccinations is less than the infection rate of disease $r < \pi_0$, the result of CSNE is uptaking vaccinations with the probability $0 < P^* < 1$. P^* is the unique solution of the equation $\pi_{P^*} = r$, which can be calculated by such function as follows:

$$P^* = 1 - \frac{1}{R_0(1-p)}. \tag{26}$$

4.1.3 Model analysis on Nash Equilibrium

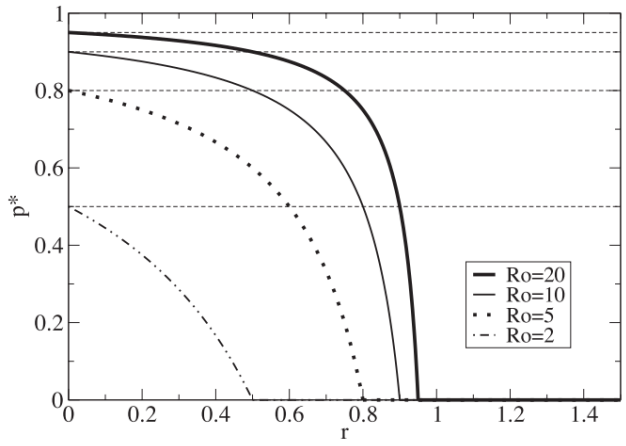

Figure 7: Vaccine coverage p^* at the CSNE versus relative risk r.

In the fig. 7, it shows that different disease with different values of the basic reproduction R_0 have different values of the vaccination threshold p_{crit}. For $R_0 = 2$, $p_{crit} = \pi_0 = 0.5$, for $R_0 = 5$, $p_{crit} = \pi_0 = 0.8$, for $R_0 = 10$, $p_{crit} = \pi_0 = 0.9$ and for $R_0 = 20$, $p_{crit} = \pi_0 = 0.95$. For any relative risks as

$r > 0$, the expected vaccination level P^* is definitely lower than the threshold value. Under the same vaccine relative risk, the disease with the higher R_0 have a high coverage level of vaccination. When the vaccine relative risk equals to 0, $r = 0$, there has the largest vaccination rate; as the vaccine relative risk increasing, vaccination level decreases; when the relative risk is big enough as the value is greater than 1 or greater than the π_0, $r \gg 1$, vaccination level equals to 0, namely individuals will not vaccinate. For childhood diseases R_0 $(5 < R_0 < 20)$, we can get that the value of the vaccination threshold, which is closing to 1, shows in generally the children disease vaccination uptake level is high. Considering actual reasons according to immune systems of children, it is not perfect and does not have enough abilities to resist diseases. It is necessary to take vaccinations to newborn children.

Let us considering the influence of the relative risk on changing vaccination strategies. During the time of the vaccine scare, the relative risk will increase. It will affect the vaccination level of the population. According to the previous analysis, if $r < \pi_0$, individuals consider vaccinations with the probability of P; if $r > \pi_0$, individuals do not vaccinated. With different new CSNE P' and P, P' is associated with the perceived relative risk r' and P is the CSNE associated with the relative risk r. According to values of the payoff gain always are positive, the value of the payoff gain ΔE measures the incentive to switch from the value of CSNE as P to the value of CSNE as P.

When the vaccine safety incident happening, the perceived relative risk r' must increase in fig. 8. The different lines show us the relationships between the vaccine risk r' and the ΔE, and between the vaccine risk r' and ΔP with different values of R_0, correspondingly different values of threshold value of vaccination

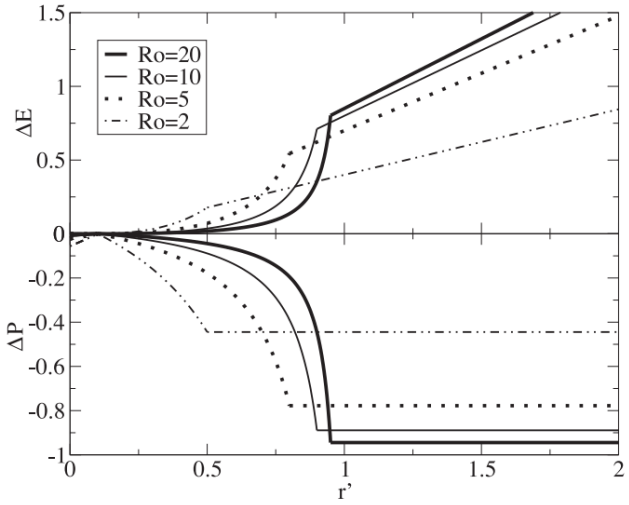

Figure 8: Analysis of vaccine scares.

level $p_{crit} = \pi_0$, which was got early. As the vaccine risk r' increasing, ΔE exponentially increases and ΔP exponentially decreases until $r' = \pi_0$. For $R_0 = 2$, when $r' \in (0, 0.5)$ with the constraint by $\pi_0 = 0.5$, ΔE increases exponentially and ΔP decreases exponentially, and then when r' increases exceed 0.5, ΔE increases as a slower trend and ΔP decreases as a slower trend. For $R_0 = 5$, the turning point gotten when $r' = 0.8$ by $\pi_0 = 0.8$, after that ΔE increases as a slower trend, but faster than the situation, when $R_0 = 2$, and the turning point of $\Delta E(R_0 = 5) = 0.52$ higher than $\Delta E(R_0 = 2) = 0.52$, the turning point of $\Delta P(R_0 = 5) = 0.69$ higher than $\Delta P(R_0 = 2) = 0.45$. And for $R_0 = 20$, when $r' = 0.95$, ΔE increases exponentially. With the increase of $r' > 0.95$, ΔE with $R_0 = 20$ increases as a slower trend than the previous process but better than the disease with $R_0 = 2$. For different R_0, ΔP decreases exponentially with $r' < \pi_0$. When r' increase to 0.5, ΔP decreases exponentially. When $r' \geq 0.5$, $\Delta P = P$. It means that when the relative risk is greater than π_0, individuals choose not to vaccination and the population proportion is as a trend of declining.

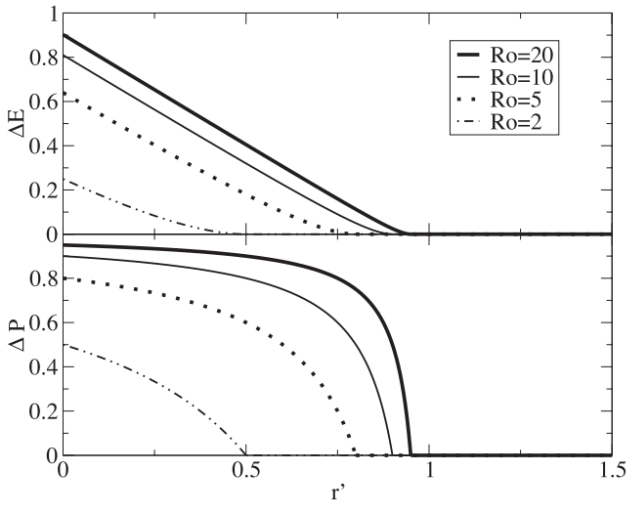

Figure 9: Public education programs impact counteract vaccine scares.

Vaccine safety issues does make much confusions to a lot of people about the vaccination. However there is no denying that vaccination is still by far the most effective method of preventing disease outbreaks. Although vaccine safety events have the bad influence on the public's perception of vaccination, people's cognition will get change by the popularity of the public education project. The curve in fig. 9 presents relative risk gradually reduce with the popularity of public education programs after the vaccine panic. That is the process occurs from $r > \pi_0$ to r', with the means less than π_0.

During the vaccine safety incidents, perceptive relative risk increasing is greater than the disease infection rate $r > \pi_0$. With the popularity of public education programs, relative risk gradually reduces, $r' < \pi_0$.

It is obviously shown that different curves have same trends. For one line, with the increase of risk of vaccine r', ΔE exponentially decreases and ΔP exponentially decreases. Until r' increasing to π_0, (different diseases have different infection rate, corresponding to different π_0), ΔE reduces to 0, ΔP also

reduces to 0. On the contrary with r' drops from π_0 gradually, within the scope of the greater than π_0, due to r and r' all are larger than π_0, so individual dose not choose to vaccination, $\Delta P = 0$; With the public education reducing the relative risk, r' gradually drops under π_0 in the process, the population vaccination rate increases gradually, that shows as an exponential trend. Comparing with the process of vaccination panic, under the help of the public education programs, the increased degree of the vaccination level is much slower than the reductive degree when vaccine panic. When relative risk is eliminated eventually, the overall level of vaccination keeps as a low state than the previous state.

4.2 Investigation on Vaccination Behavior in Social Networks

Vaccine inoculation is recognized as an outstanding achievement in biomedical areas and public health areas in the 20th century. Vaccination is a successful production preventing for preventing some epidemics spreading among population. Many infectious diseases, such as smallpox, have already been effectively controlled. From the 16th century to the 18th century, the number of people died each year from smallpox was about 50 million people in Europe and about 80 million people in Asia. Roman Empire decayed in the 2nd century and the 3rd century legend because of the ravages of smallpox, which cannot be curbed. But now smallpox has completely been eradicated in the world [23]. These successful cases depend on not only the effective vaccine but also the implement of the planned prophylactic vaccination. Those cases has proved that the specific vaccines can prevent some epidemics from population and take some epidemics spreading under control. But in terms of some other disease, which is not easily controlled, even with a specific related disease vaccine, if the vaccination rate maintains a low level, a well prevention of the epidemic spread can still not be realized. In the real case of immunization programs to hepatitis B, although the hepatitis B (HB) vaccine has already have a quite mature development, which means that many hepatitis B vaccine can efficiently prevent hepatitis B, the actual incidence of HB remains high for a time due to gaps in coverage persist. According to the data of survey in 2015, there are 120 million people infected with HB in China, Where chronic hepatitis B patients about 30 million cases. About 35 million people die each year from diseases associated with chronic hepatitis B. Therefore an efficient measure, which makes an effective strategy or a policy involving improvements of the population vaccination rate is the key

to prevention works.

In the article "imitation dynamics of vaccination behavior on social networks" written by Feng Fu, Daniel I. Rosenbloom, Long Wang and Martin A. Nowak (2011) authors consider an issue about research the social vaccination behavior in definite population groups [7]. Decisions of individuals behaviors about whether to take up vaccinations decide the population vaccination rate. Scholars in their investigation propose a model that not only would measure the probability of vaccination take-up within a definite social network but it takes into account the phenomenon of the anecdotal information implicit influence in making vaccination choices as well.

It is necessary to note that an individuals vaccination and, thus, immunity status contributes to the whole populations immunity. The more individuals decide to take up a voluntary vaccination, the higher is the chance to escape an infection risk to those who lay their hopes on the consciousness of the other society members and preferred not to bear any vaccination costs by themselves. In our investigation papers we call them "free-riders". In fact we should admit that "free-riding" is the most favorable scenario this kind of behavior bears no costs at all. However, irrational but successful example of those "free-riders" gives a green light to their social neighbors and in the next epidemic round when much less members would take up a vaccine, herd immunity would evidently plummet and suffer under the epidemic outburst. Thus, this work highlights the effect of the imitation behavior and its consequences on the whole nation health.

On one hand, it is obvious that pre-emptive vaccination can save us from the great variety of possible diseases and their adverse influence on our health.

On the other hand, each of us faces definite rational and irrational arguments why he or she may not take up a vaccination. Rational reasons for the vaccine rejection underlie in its cost that involves in its turn financial costs, temporal costs and probable adverse costs caused by a vaccine on the individuals health status. Irrational motives include probable anecdotal information, public fears, personal examples of the close friends and relatives. If we assume that individuals act rationally and with perfect knowledge of their infection risks, then public vaccination decisions would obviously converge to a Nash equilibrium. Nevertheless, irrational variable in peoples behavior leads to inadequate level of the vaccination coverage in the community. Let us take down to the proposed model and its methods.

4.2.1 Description of the SIR model and its methods

Before the main method, we make the introduction of the social network. In recent years, as the rise and development of the complex network research, it makes the people have a clearer understanding of the structural evolution and the complexity of various networks in reality. Especially in 1998, Watts and his supervisor Strogatz published an article in Nature about the small world network model [23]. The researches of complex networks quickly attracted attentions of many researchers in different fields, such as the physics and the biology, complex network theory has been full of exploration and development.

Complex network theory provides the convenient frameworks for describing the relationship of games among individual. The nodes in the network represent individuals in game. The sides represent the relationships between individual and his neighbors in the game. In this way, we can use topological

relations of the complex network to study the complex game. The well-mixed assumption of the game theory can be viewed as the total connected graph. The game with two dimensional lattice or one dimensional ring can be converted to the regular network game. However, in the real world networks are heterogeneous as the most number of neighbors are different. Therefore, it is significant to research the impact on the heterogeneity of the network of contacts to the dynamics game [16].

To study the voluntary vaccination dilemma the authors take as a basis a simple agent-based model in the spirit of evolutionary game dynamics. This model in its turn is combined with the susceptible-infected-resistant (SIR) model, or epidemiological model. The first definition of SIR model is presented by Kermack and McKendrick in 1927 [2]. In this model the population is divided into three categories: susceptible, infected and resistant ones. Susceptible population includes uninfected individuals but lacking the immune ability to diseases, who will easily turn to be infection after contacting with the infected persons; Infective population includes infected individuals, and they could influence from the susceptible part; Removal population includes to healthy individuals, which are recovered from infected individuals. For well-mixed populations, the time evolution states can be expressed by following functions [25]:

$$\begin{aligned} \frac{dS}{dt} &= -rNSI, \\ \frac{dI}{dt} &= rNSI - gI, \\ \frac{dR}{dt} &= gI, \\ S + I + R &= 1. \end{aligned} \tag{27}$$

Where r means the disease transmission rate, and g means the rate of

recovery from infection. N is the total population size.

Denote rN/g by R_0, commonly called the basic reproduction radio. Dividing eq. 27 by eq. 28, there obtains a function that

$$\frac{dS}{dR} = -R_0 S. \tag{28}$$

Using the initial condition $S(0)$ 1 and $R(0) = 0$, the final state $I(\infty) = 0$ and $S(\infty) = 1 - R(\infty)$, and $R(\infty)$ is the final fraction of individuals who had been infected during the epidemic outbreak, we obtain

$$R(\infty) = (1 - e^{(-R_0 R(\infty))}). \tag{29}$$

If we consider preemptive vaccination by supposing that a proportion x of the population initially vaccinated, eq. 29 can be rewritten as

$$R(\infty) = (1 - x)(1 - e^{(-R_0 R(\infty))}). \tag{30}$$

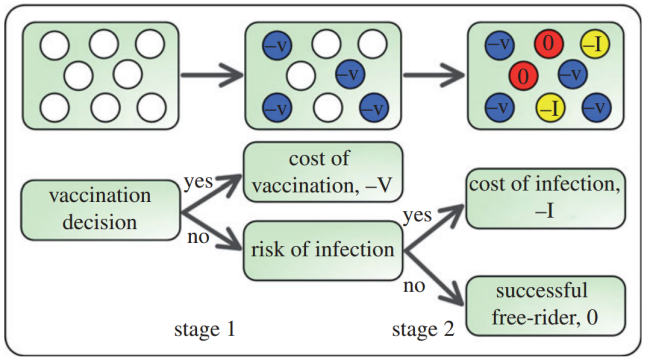

Figure 10: Two-stage game.

The experiment is held within one epidemic round as vaccines are mostly effective for only one season due to the capability of the pathogens to evolve mutation and adapt to the vaccine. Authors model the vaccination dynamics as a two-stage game in fig. 10. For simplicity, we assume that any of the vaccine applied would be highly efficient and protect the individual from the probable infection risk. The first stage represents a public vaccination campaign that ordinarily takes place before any epidemic occurs. The necessary admissions: X is a fraction of vaccinated individuals; the cost of vaccination in general should be substantially lower than the infection cost. This is a period when each individual thinks carefully about his personal pros and cons whether to take up a vaccine or deny and makes his final decision in this epidemic round. If a decision is made to vaccinate, a definite cost of the vaccination V is taken by the vaccinated individual.

The second stage depicts the process when unvaccinated individuals can be subdivided into two categories. One of them is that those who face the infection risk and bear infection cost I (that includes healthcare expenses, lost productivity and even probability of lethal outcome), and those lucky ones unvaccinated called free-riders, but nevertheless, not infected. In other words, free-riding is the phenomenon when unvaccinated individuals remain healthy and benefit from the vaccination consciousness of the others. In our model, the epidemic initially infects individuals I_0, and then spreads according to the SIR dynamics model with per day transmission rate r and recovery rate g. Conclusion of these two-stage game is the following: the highest benefits get those unvaccinated participants who managed not to get infected within the epidemic round. Thus, each individual wants to escape both vaccination and infection. Besides,

successful examples of unvaccinated individuals and personal fears linked with some isolated cases influence much on him. However, group interest lays just on the opposite side, that the more individuals would get vaccinated, the more solid immunity to the society would be provided.

The assumption of rationality is relaxed in this model. From the evolutionary perspective individuals revise their vaccination strategy each season basing on the current payoff. Besides, we assume that individual i randomly chooses individual j from their common network as a role model. Clearly, the strategy with the higher benefits will be likely to be copied in the next season. Thus, here the author introduces the variable β standing for the strength of selection. For small value of β (weak selection) individuals are less responsive to payoff differences. In other words, individual may choose a strategy of a less successful role model, and interact more rationally not only retrospectively but with some definite future expectations. Large β stands for the behavior model, when individuals keep to the strategy with the higher observed payoff, even if the payoff difference is relatively negligible. An individual i randomly chooses a neighbor j. We suppose that the probability that individual i adopts individual js strategy is given by the Fermi function

$$f(P_j - P_i) = \frac{1}{1 + exp[-\beta(P_j - P_i)]}. \tag{31}$$

It means that individuals choose a strategy dependent on the neighbors behaviors and is decided by the difference of payoff. And in this function denotes the strength of selection where $0 < \beta$.

4.2.2 Results and Conclusions

In the Fig. 11 and Fig. 12, it shows vaccination dynamics and epidemic dynamics in well-mixed populations. Lines of open and filled squares and open inverted and filled inverted triangles mean simulation results. For open squares and open inverted trangles, $\beta = 1$; For filled squares and filled inverted trangles, $\beta = 10$. Lines of dotted line and solid line show theory results. For dotted line, $\beta = 1$; for solid line, $\beta = 10$. The horizontal axis is the relative cost of vaccination c.

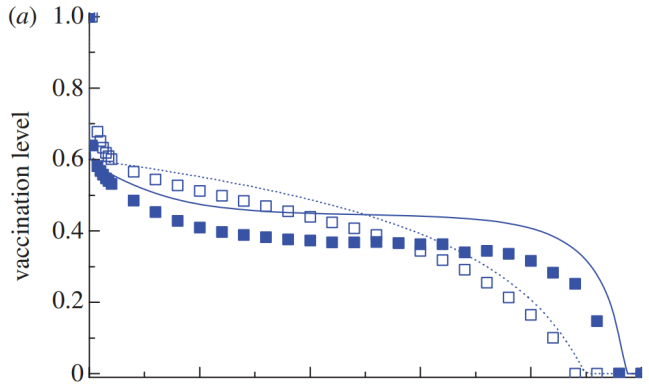

Figure 11: Vaccination level dynamics in well-mixed populations.

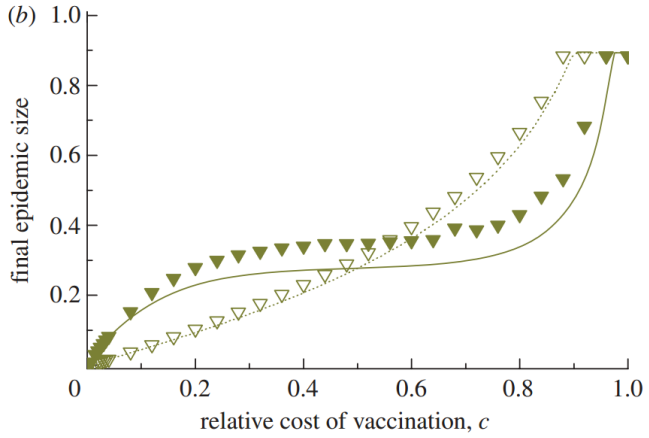

Figure 12: Epidemic dynamics in well-mixed populations.

For the curve in well-mixed population, with $\beta = 10$, when increasing the cost c the vaccination level have a drop from the initial vaccination level 0.70. The curve has a stable 0.38 with the relative cost of vaccination $v = 0.20$. Then the curve from $v = 0.75$ to $v = 1.0$ drops to vaccination level 0. For the same value of β, the final epidemic size has a increasing trend from 0 under the vaccination level 0.70. The epidemic curve increases to a stable state 0.38 under the vaccination level 0.38 and $v = 0.20$. Then with the increasing cost the epidemic size closing reaches to 0.90. The two graphs above have a same stable range with the relation cost of vaccination $0.20 < v < 0.80$. When $\beta = 1$, the value of vaccination level and epidemic size have a stable trend like a straight line decreasing from the initial point to final vaccination level 0 and increasing to final epidemic size 0.90 with the increasing relative cost of vaccination from 0 to 1.0.

In lattice populations, Fig. 13 and Fig. 14 show vaccination dynamics and epidemic size dynamics. Open squares with the solid line and open inverted triangles with the solid line have $\beta = 1$; filled squares with the solid line and filled inverted triangles with the solid line have $\beta = 10$. The horizontal axis is the relative cost of vaccination c.

For the curves in lattice population, when $\beta = 10$, as increasing cost the vaccination level straightly drops from the initial level 1.0 to a stable 0.1 under the relative cost of vaccination $v = 0.27$. Then have a long stable state until $v = 0.75$. After adding the relative cost the vaccination level drops to 0 with the relation cost of vaccination $v = 0.87$. For the same value of $\beta = 10$, the final epidemic size have an increasing trend from 0 to 0.60 respectively with the vaccination cost $v = 0$ to $v = 0.27$. Similar with the vaccination level, final

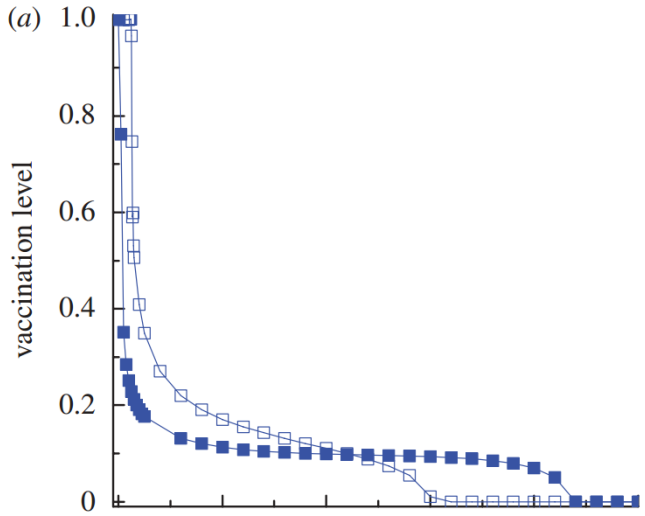

Figure 13: Vaccination level dynamics in lattice populations.

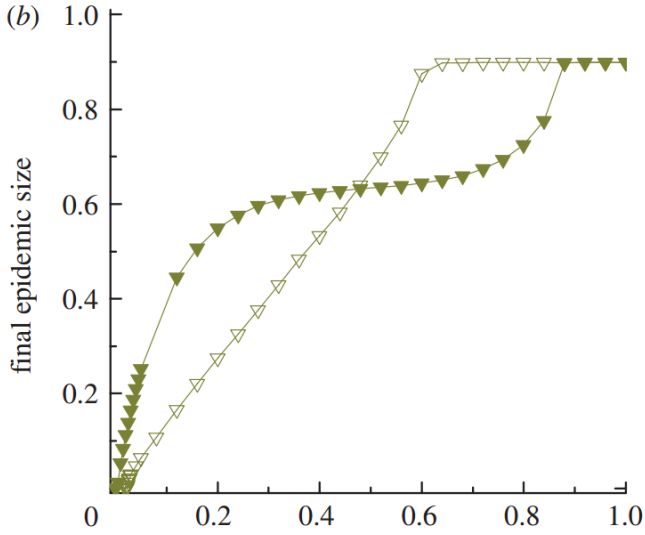

Figure 14: Epidemic dynamics in lattice populations.

epidemic size have the same cost value $v = 0.87$ increasing to 0.90. With $\beta = 1$, the value of vaccination level straightly decreases and until vaccination cost $v = 0.60$ decreases to 0. For $\beta = 1$, the final epidemic size have an increasing trend from 0 to 0.90 with the interval of vaccination cost from $v = 0$ to $v = 0.60$. And with increasing the relative cost of vaccination, the final epidemic size stays 0.9 under the vaccination level 0. In lattice population, simulations and theory

are same.

For the Fig. 15 and Fig. 16, they show trends of vaccination dynamics and final epidemics size dynamics in random network populations. Open squares with solid line and open inverted triangles with solid line have $\beta = 1$; filled squares with solid line and filled inverted triangles with solid line have $\beta = 10$. The horizontal axis is the relative cost of vaccination c.

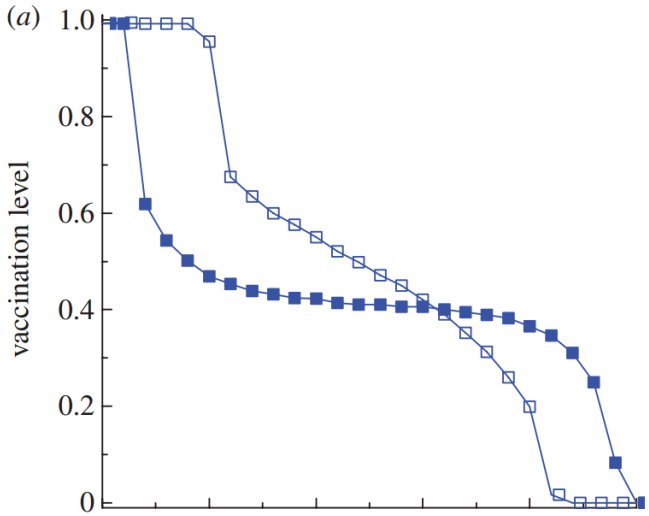

Figure 15: Vaccination level dynamics in random network populations.

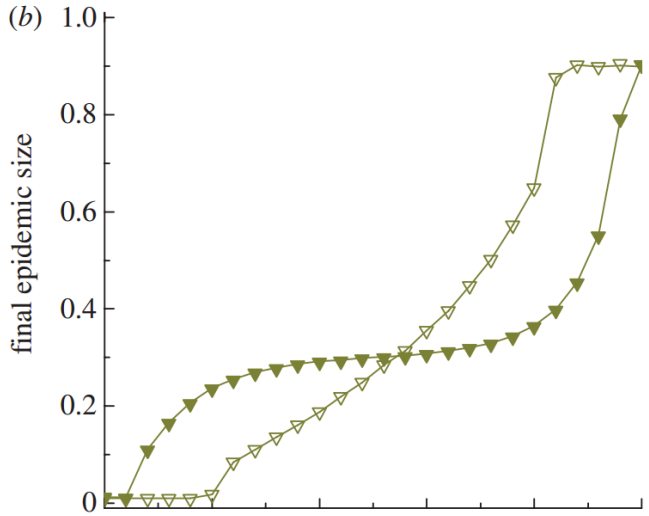

Figure 16: Epidemic dynamics in random network populations.

For these curves in random network populations, the simulations and theory are same. With $\beta = 10$ as the increasing cost v the vaccination level straightly drops from the initial value 1.0. Then keeping to a stable 0.40 when an interval of the relative vaccination cost $0.34 < v < 0.80$. Finally it drops to 0 with increasing the relation cost of vaccination from 0.8. For $\beta = 10$, the final epidemic size have an increasing trend from 0 when the vaccination cost $v = 0.04$. Then the vaccination level keeps to a stable state 0.30 when the vaccination cost $v = 0.35$. The two graphs between vaccination level and epidemic size have a similar stable range with the interval of the relation cost of vaccination $0.35 < v < 0.60$. When $\beta = 1$, the value of vaccination level do not move before $v = 0.20$. Increasing the vaccination cost from $v = 0.20$ the vaccination level straightly drops to 0 until the relative cost of vaccination $v = 0.85$. With the same value of $\beta = 1$, the final epidemic size also does not have any changes in the interval of the relative cost of vaccination from 0 to 0.20. Then the final epidemic size have an increasing trend from 0 to 0.9 under the vaccination cost from $v = 0.20$ to $v = 0.85$. As increasing the relative cost of vaccination until $v = 1.0$, the vaccination level maintains 0.90 under the vaccination level 0.

Comparing the graphs, we see slightly changing value of c enlarge with the β(strength of selection). In the random network populations the trends could be controlled well enough when the cost c is located in a small range. But with the increasing cost c the trend gets out of control. Basing on the initial data used in the investigation, we can get following curious conclusions: in the vaccination game, if all of ones neighbors adopt one strategy, it occurs to be beneficial to use the opposite strategy. By this reason vaccinated and unvaccinated individuals change their roles throughout the experiment.

For small value of β (weak selection) we see that the function is roughly linear, the higher is the vaccination cost, the less individuals would take up a vaccination. Therefore, as vaccination level falls with the growing cost, the final size of the epidemic grows. There is a point on the graph indicating a relatively high level of vaccination cost, above which no one chooses vaccination and the epidemic reaches its maximum size. As for the large β (strong selection) results we see that individuals will rather attempt to "free-ride" than adopt a rational decision. And this kind of irrational and imitating behavior reflects on the graph correspondingly. It is notable that if we restrict interaction between an individual and his neighborhoods, we can partly eliminate the "free-riding" syndrome, but instead we get a higher sensitivity to the parameter of the cost of vaccination, c. Thus, restricted spatial interactions can provide us with results close to Nash equilibrium optimal to the social wealth. On both our graphs we can allocate the point defining the critical vaccination cost below which the epidemic is prevented.

The next notable conclusion is that higher vaccination coverage is typically required to achieve herd immunity in populations with greater degree of heterogeneity. Particularly, degree of population heterogeneity defines many aspects of social behavior. Thus, we can assign so called social "hubs", or important social centers of great influence on the neighbors. These are, for instance, physicians, teachers and many others occupied in the social sphere. Such "hubs" are likely to get vaccinated because of the wide range of interaction and therefore they are subject to greater risk of getting infected. In their turn, "hubs" can spread disease to a great number of peers if infected. And vice versa, hubs government policy vaccination plays a dramatically significant role in disease prevention.

Thus, the considered above investigation shows how anecdotal information and public fears affect our social behavior and form strong selection imitating model. In the whole society scale, such irrational behavior responds for the vaccination coverage fall below Nash equilibrium. It is a question if a voluntary vaccination really makes sense in our liberal society on condition that the majority prefers the strategy of "free-riding", contradicting the whole society's interests. One can compare the voluntary vaccination to public goods studies as herd immunity provides a communal benefit. However, here we should relax the assumption of rational behavior of individuals and mind that public fears can significantly influence on vaccine take-up and public health.

5 Discussion

In "World Cancer Report 2014" published by WHO [26], there were 14.09 million of malignant tumor incidences in the whole globe in 2012, including 7.43 million male patients and 6.66 million female patients; and there were 8.2 million people died from different kinds of cancers, including 4.65 million males and 3.55 million females. The most common cancer was lung cancer, accounting for 13% of the total. The second was breast cancer, accounting for about 11.9%. Then there are colorectal cancer, prostate cancer, stomach cancer, liver cancer and so on. In cancer deaths patients, lung cancer occupied the first place, accounting for about 19.4%. Next is liver cancer, accounting for about 9.4%. Then followed by gastric cancer, there are colorectal cancer, the breast cancer and so on. In China, according to the national cancer center about the statistical report of the latest status of cancer, there pointed out that the cancer rate in China was 0.55%. According to the data in 2011, it showed that the number of cancer patients was 3.37 million, including 1.91 million men and 1.45 million women. Among the top 10 of malignant tumors, the top three about male are: lung cancer, stomach cancer and liver cancer, while for females they were breast cancer, lung cancer and colorectal cancer. With the rapid development of science and technology, cancer is a difficult risk for people because of the lack of an effective method making people puzzling. It seems be sentenced to death once having a cancer [12].

Thankfully, the cancer treatment in the last decades has made some new progresses. For the treatment of tumors in addition to the surgical removal of the entity lesions, the chemotherapy, the radiation therapy and the targeted drugs are widely used. To some extent, these methods can control the development of

cancer. However there exists many subsequent problems in the process of the treatment. To the chemotherapy or the radiation therapy, due to lacking the specificity, drugs not only kill tumor cells but also kill normal cells, thus have a large toxicity and damage the immune system, seriously affecting the patient's quality of recovery. Then researchers put forward the targeted drugs with strong specificity for cancer. Targeted drugs can targetedly kill tumor cells with certain genetic mutations without hurting normal cells. But it also has limitations due to only specific mutation patients can benefit from such targeted drugs. More importantly, however, cancer cells can often evolve a variety of mechanisms to combat these drugs, namely we often say the resistant. According to these factors, the cancer development of some patients has been effectively controlled at the beginning of the treatment, but soon after be relapsed again.

In recent years, researchers have proposed new treatments based on the characteristics of the body's own immune, which was called immunotherapy. It appears to be effective to solve the shortage of the previous treatment. Immunotherapy is used by activating the body's own immune system to kill tumors. This method is considered can effectively kill tumor cells, inhibit tumor evolution, and effects are relatively mild and controllable, and the recurrence rate is low.

In a wide variety of cancer clinical trials it shows a surprising result and brings hope to the vast number of cancer patients. For the normal immune system, the immune system in the human body always plays in charge of recognizing and eliminating the bacteria, viruses and other pathogens for protecting the body from damage, ensuring the normal operation of the body.

Normal immune system has an effective mechanism for distinguishing be-

tween the pathogens and the molecular of the body's own. It can selectively eliminate these pathogenic factors without hurting the bodys own molecular. In the process of recognition, there is a certain type of signaling molecules to prevent the immune system attacking the body's own molecules, called immune checkpoint. Some of them can activate the immune response, and some others can suppress the immune response. If immune check points have problems, the immune system will be unable to distinguish between the external factor and the internal factor, then lead to the immune system attacking the normal tissues and cells. When the human body cell gene have the mutation because of various factors, the accumulation of these mutations finally cause cells out of control, also known as cell cancer.

At this time due to the cancerous cells have some characteristics molecules different from normal cells, such as cancer gene mutation, the immune system will start to recognize and eliminate cancerous cells. However, according to the mutation rate with extremely high, in the face of the cleaning function of the immune system, the cancer cells will not give in easily, and will change their own recognition characteristics, evade the identification of the immune system. This mechanism is called immunosuppressive or immune escape. Once the cancer cells evade from attacking of the immune system, the cancer cells will crazily breeding and occupy other tissues and organs, and out of control. Therefore in the face of the limit resulted from chemotherapy drugs, the combination with the person's own immune system, known as the application of immunotherapy, has brought hope to cancer patients. Currently in clinical the immunotherapy mainly includes two categories: cell therapy and intervention therapy.

However, like any kinds of therapies, Immunotherapy is not perfect. Im-

munotherapy fights cancer by activating the body's own immune system. In clinic, if the control of the activated immune system is not very well as too active, it may harm to normal cells, causing immune related side effects, and more seriously causing organ failure even death. Therefore, groping for the right dose of drug and using the right medication to control these side effects are particularly important.

According to the models applied the G-function created by Jessica J. Cunningham, Robert A. Gatenby and Joel S. Brown creates (2011) [6], it provides an important tool for the cancer treatment. The model can get the resistance trend of cancer cells and population density trend of cancer cells under the drug dose and environmental parameters. According to the corresponding analysis of different doses of the trends, and the analysis of the resistance development trend, there can find the right delivery time and optimal dose of drug. To a certain extent, it can simulate in theory, get the quantitative analysis of direct effect of drugs on cancer cells, and provide a method to evaluate cancer therapies.

Now the effectiveness of the immunotherapy of lung cancer has been tentatively identified. The research of the immunotherapy of non-small cell lung cancer showed that the efficacy of monoclonal antibodies for advanced NSCLC has a clear curative effect, such as can solve the problem of allergies and adverse reactions. The immunotherapy of the monoclonal antibody is expected to become the standard supplementary treatment of the lung cancer and to enrich the content of comprehensive treatment of the lung cancer. The method, which is presented by Jessica J. Cunningham, Robert A. Gatenby and Joel S. Brown (2011) [3], can be used to simulate the effect of monoclonal antibodies for the

treatment of the lung cancer, and simulate the trend of cancer cells resistance for analyzing the effective treatment and providing an important basis for clinical trials.

In another aspect, there is an application about combined therapy. According to the multi-drug therapy presented by monitoring the changing trend of cell resistances, Jessica J. Cunningham, Robert A. Gatenby and Joel S. Brown (2011) [3] put forward the multi-drug therapy combined immunotherapy and the traditional radiation or the chemotherapy or the targeted therapy for the study of controlling cancer. Aiming at the resistance due to the immune escape in immunotherapy, the model of multi-drug therapy can develop the targeted combined cancer therapy of treatments, such as combining cancer immune suppression mechanism for improving the success rate of the treatment. In the combination of immunotherapy and traditional radiation or the combination of immunotherapy and chemotherapy scheme, firstly during the first phase of the immunotherapy it stimulates the immune system, which relying on the immune function reducing cancer cells and at the same time, to some extent weakening the resistance of cancer cells making cancer cells becoming vulnerable. It benefit the second phase of chemotherapy drugs.

The effects of drugs under such conditions greatly enhance and eliminate most of the cancer cells. This method do not eradicate cancer, but according to the results of the research, comparing with the general single therapy, the combined multi-drug therapy can control the population of cancer cells at a lower level. With the increase of the further research and clinical experience, there will be more mature and perfect immune therapy to help people cope with various kinds of cancer and benefit the patients.

China as such a large social group with a big country with 1.3 billion people, nearly closing to a quarter of the total population in the world when facing the outbreak of the influenza and other infectious disease often feels helpless. Due to the large amount of population, the high rate of the population mobility and the complex and diverse social structure, once happening the epidemic outbreak the rate of the outbreak will be difficult to be effectively controlled in China. In the 2003 SARS outbreak case, there were $5,327$ of cumulative cases in China, and the death of 349 people; in the whole world there were $8,069$ people infected and 775 people died from SARS. In the 2009 flu pandemic, there were $120,498$ people infected and 648 deaths in China from the H1N1 flu and the global number of infected person is $1,353,141$ and death person is $15,934$. Statistic data shows that China has made "outstanding contributions" to the world epidemic outbreak situation. Therefore the epidemic control in China plays an important role in the global epidemic outbreak.

The development of an effective and timely outbreak control program has to be solved as a major and important issue. Influenza is an acute febrile respiratory disease caused by influenza viruses. In history there were many cases of the flu outbreak all over the world. The influenza is caused by various kinds of influenza viruses.

In some given years of the outbreak, some species of the influenza virus may become extinct, but some other species of the influenza virus are generated over time or become mixed virus with the mixed generation of other types of influenza viruses. Since the influenza viral antigens mutate frequently, they could easily lead to repeated infections and high incidence of populations. Therefore these flu viruses can cause the influenza pandemic. Generally, to the influenza

season of a year in North and South, the variations of influenza viruses cause about 50 million deaths in the world. In these variations, some newly created viruses of variations are milder treated as a general epidemic. Besides, some other types of the newly created viruses are more serious viruses that can cause a significant influenza pandemic. For the infected person, some complications of the influenza seriously threat the human health, such as pneumonia, otitis media, rhinitis, myositis, Leiyi Shi syndrome and other serious complications.

So comparing with the common cold, the influenza has more severe symptoms, more contagious ability and are useless to the antibiotic therapy. Although influenza is difficult to be cured, it can be prevented by vaccinations. The influenza vaccination is a most effective method to prevent the flu outbreak. Therefore, there is a growing emphasis on the study of the influenza vaccine. Influenza vaccine is used for the prevention of the influenza, and applies to any healthy people with the possible opportunity to be infected by influenza viruses. In the policy of vaccination, people should better take one dose before the epidemic season annually and the immunity sustainable will maintain one year.

As one of the main measures for the prevention and control of influenza, the influenza vaccine can reduce the chance of infection or alleviate the symptoms of influenza. The study of influenza vaccine has received an effective progress. We have already developed results about the flu vaccine for seasonal flu outbreaks. WHO has estimated that in May 2009, according to assumptions about the best scenarios, the global annual production capacity of the pandemic influenza vaccinate is about 5 billion. But thereafter, according to more real information obtained by the real vaccine production and the appropriate dosage of vaccine area, now the estimate of WHO makes that the annual production

capacity of the pandemic influenza vaccine in the global is about 3 billion. This figure is less than previously estimate. These vaccine is still not enough to supply and cover 6.8 billion of the world's population. Almost everyone in the world has a susceptibility to the regular development of the highly infectious virus. Now the vaccine supply can be protected the number doubled.

As the global capacity for influenza vaccines is limited and cannot meet the demand problem and the flu vaccine is an important preventive strategy, the effective vaccination strategy is an effectively method to improve immunization rates in the general population under such limited condition of vaccines. For a country with low population density like Russian, epidemic is not easy to spread and the herd immunity is easy to realize. Different with these low population density countries, in China even for a general small city, the social network of the small region is complex as closing 0.5 million people. The social structure in the small region is similar considered to a scale-free network [1]. In China for a social group, according to the more complex social structure, people become vulnerable to be attacked by viruses. Therefore epidemic is easily transmitted among the social group. It is necessary to develop an efficiency strategy of immunization.

In the book of "the complex network theory and application", it introduces five immunization strategies: the random immunization, the immunization target, the acquaintances immunity, the cyclic immune and the contact tracing. Feng Fu, Daniel I. Rosenbloom, Long Wang, and Martin A. Nowak investigates the vaccination behavior on social networks under the condition of the vaccination cost [19]. They provided a useful method for researching the effect of vaccination behavior in different social networks. The random immunity refers

to randomly select some people immunize. Under the random immunization strategy, in order to achieve the herd immunity, all population need to take up vaccines. It is realistic to a small group rather than a large size group with the large amount of population. The target immunity refers to a selection of nodes with a large degree to be immunized. After immunizing these nodes, it means that relatively large number of people around these nodes reduce the way to exposure to the virus and then prevent the virus infection. It is an efficient way to a social network with a low population mobility like a closed small village or an area with a low population density. The acquaintance immunization strategy refers to randomly find a node and a neighbor of the node to immunization. Acquaintance immunization strategy is the most effective of local immunization. The ring vaccination refers to isolate or immunity all neighbors of infected individuals.

There is a real application, which is Ebola vaccine for clinical trials, adopting the ring vaccination strategy. By isolating all possible individuals contacting with the Ebola virus infectors and vaccinating the isolators, there formed a "ring isolation zone" surrounding Ebola virus infectors to prevent further spread of the virus. The clinical trial results showed that this strategy ensures a very significant effect of control of the vaccine for Ebola virus [24]. The ring strategy of Ebola vaccine got tested in the real Ebola case. This strategy has also been used in the smallpox virus prevention. The contact tracing refers to trace those who have contact with contagious individuals, then vaccinate with a certain probability. Efficient contact tracing and testing made it possible to conclude, with authority, that the outbreak was over in record time. In the outbreak of SARS, the date has shown that SARS has been controlled using conventional

measures such as rapid detection, infection control, isolation, quarantine and contact tracing [5]. The imitation dynamics of vaccination behavior is a good way to simulate the epidemic dynamic before the epidemic outbreak and specifies a valid immunization strategy provided to prevent the epidemic spread.

According to "vaccination and the theory of games" written by Chris T. Bauch and David J. D. Earn and "imitation dynamics of vaccination behavior on social networks" written by Feng Fu, Daniel I. Rosenbloom, Long Wang, and Martin A. Nowak, there are two integrated model combining the epidemic model, as called SIR model separately related to the vaccination cost and the vaccination risk [19]. They are helpful to the development of the vaccination policy according to predict the trends in the epidemic under different conditions.

We analyze different approaches applied game theory methods from new perspective such as dynamic, adaptive and self-regulating to explore the structural characteristics of the population and how does the limited rationality of individuals impact an individual's immune behavior. Then from the theoretical level state the study discusses the underlying mechanisms about switching population immunization rates from a low level of "Nash equilibrium" to global optimization state of. Through this research we try to estimate a new immune method to solve immune problems based on evolutionary game theory, explore mutual coupling and co-evolution of the spread of infectious diseases and immunity behavior from a new angle, study physical phenomena and laws, which are reflected in the true complexity of the system, to help to understand movement patterns in complex systems and provide a theoretical reference for measuring policy issues about the prevention and control of infectious diseases and the way of vaccine distribution for real social systems.

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