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A Novel Approach to Optimize Combinatory Drugs Using Markov Chain

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***Abstract*—Combinatory drugs are often used in clinical medications for treating some complex diseases such as cancer, diabetes, etc. An extreme challenge in combinatory therapy is that the number of combinations will increase exponentially as the types of drugs increase, which makes it very difficult to choose the optimal concentration. In this paper, we present a new algorithm based on the stationary distribution of Markov chain to optimize combinatory drugs. We evaluated the new algorithm by comparing its performance with the other two stochastic algorithms, the Gur Game algorithm and the modified Gur Game algorithm. Numerical simulations clearly show that the algorithm based on Markov chain has a better performance than these two stochastic algorithms, in terms of both reliability and efficiency. This work provides a general method for the combinatorial optimization problem, and it is meaningful for clinical combinatory therapy.**

Keywords—combinatory drugs; optimization algorithm; Markov chain; stationary distribution; prediction

I. INTRODUCTION

A single drug usually cannot achieve an expected curative effect due to the robustness of organisms. However, a mixture of drugs is in general more effective than a single effector. Hence, combinatory drugs are often used in clinical medication for treating some complex diseases such as cancer and diabetes. For example, Herpes simplex virus-1 (HSV-1) is one of the most pervasive infections worldwide. The antiviral drugs used in clinical medication usually include three antiviral cytokines (IFN-α, IFN-β, IFN-γ), ribavirin, acyclovir, and TNF-α [1]. On the other hand, it is more efficient to treat multiple targets at the same time than just a single target once. Therefore it is usually the most effective way to use combinatory drugs for multiple targets at the same time in clinical therapy [1-6]. However it is extremely difficult to identify the optimal drug concentration by trial and error from the numerous possible combinations for the inherent complexity of biological systems. For example, if we just have 5 drugs and each drug has 10 levels of concentrations, we will make our choice in the space of 10^5 combinations. In other words, the number of combinations will increase exponentially as the types of drugs increase. It is impossible to make a test for each combination. Therefore, it is an important problem how to make the testing number as small as possible and predict the optimal combination as accurate as possible.

Recently, several algorithms have been proposed for predicting the optimal combinatory drugs [1-12]. For instance, Ding et al. [2, 3] reported a new application of fractional factorial design to investigate a biological system with HSV-1 using six antiviral drugs. This method of experimental design is widely used in industry and manufacturing. It was shown that fractional factorial design using two levels and three levels can screen for important drugs and drug interactions. Wei et al. [4] proposed a feedback system control (FSC) scheme using differential evolution (DE) algorithms to search for the optimal combinatory drugs. In this work, the FSC based framework can rapidly identify the best combination of components to form the optimal aptamer structure binding to a target molecule. It was shown that this approach used a very short detection time and high sensitivity could be achieved with the optimized combination. Al-Shyoukh et al. [5] introduced an approach based on neural network and linear regression models and demonstrated how mathematical learning algorithms can enable systematic characterization of multi-signal induced biological activities. The proposed approach can enable identification of input combinations to result in desired biological responses. Wong et al. [6] proposed a close-loop optimization framework guided by a stochastic search algorithm, the Gur Game, taking a random walk in a finite state automaton (FSA) [7], to predict a new drug combination that is likely to improve the cell response. Furthermore, Yoon discussed the limitations of the original Gur Game algorithm and pointed out that the performance of Gur Game algorithm relies on the underlying drug response functions and may result in suboptimal performance if the drug response $f(x)$ is not properly normalized or the FSA and the directions for rewarding (and penalizing) specific drug concentrations are not properly designed [8]. And in this work, Yoon proposed a novel stochastic optimization algorithm based on biased random walks of a FSA [8]. Unlike the original Gur Game algorithm, the proposed algorithm chooses the next state in two cases by comparing the current drug response to previous drug response and numerical experiments show that the proposed algorithm significantly outperforms the original Gur Game algorithm.

In general, the nonlinearity is the typical characteristics of the response of biological systems to multiple drugs. As discussed in [9], if the biological system of interest shows a significantly nonlinear response to multiple drug combinations, a stochastic search algorithm, such as the Gur Game algorithm, is expected to perform better than non-stochastic algorithms. One of the reasons is that the stochastic behavior prevents the algorithm from being trapped in a local optimum and increases

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the probability of finding the globally optimal drug combination. On the other hand, because the unavoidable measurement noise widely exists in experiments, stochastic search algorithms have higher robustness than deterministic algorithms. However, in some cases, the Gur Game algorithm or the proposed algorithm in [8] may degrade their overall performance on account of the shortcomings of the framework of these algorithms. In this paper, we discuss the limitations of the original Gur Game algorithm and the proposed algorithm in [8], and then proposed a new algorithm based Markov chain which can surmount the deficiencies above and achieves the goal with a wonderful performance. We also show that the algorithm based Markov chain has a better performance than those two stochastic algorithms by numerical simulations, in terms of both reliability and efficiency. Furthermore, this work provides a general method and a new idea for the combinatorial optimization problem.

II. METHOD

A. Assumptions

Before the introduction of the principle of the Markov chain method, two hypotheses are assumed as follows:

- The effect of drugs on experimental subject changes smoothly as the concentrations of combinatory drugs alter slowly.
- The number of combinations may be large, but finite.

These assumptions are very natural. Organisms under smooth input will not change tremendously. Also, the concentration of drugs always belongs to an interval, which means the number of combinations of different drugs must be finite. Under these assumptions, the optimization of combinatory drugs can be expressed in a Markov process with finite states.

B. The Principle of the Markov-chain Method

Firstly, a simple example is used to illustrate the idea for this method. To find the optimal concentration from the N possible concentrations of a single drug, let $\Phi = \{1,2,\dots,N\}$ represent the set of the levels of N different concentrations from lower to higher. Define $f(x)$ to be the normalized drug response function, where $f(x) \in [0,1]$ for $x \in \Phi$, to represent the effect of treatment. In other words, the better effect of the concentration, the higher value of the response $f(x)$. A response of $f(x) = 0$ implies that the drug is completely ineffective at concentration level x, while $f(x) = 1$ implies that the drug achieves its best therapeutic effect at concentration level x. This is a natural assumption. For example, $f(x)$ represents the percentage of cured cells infected by a virus. Our main goal is to find the optimal concentration x^* that maximizes the objective function $f(x)$ as follows:

$$x^* = \arg\max_{x \in \Phi} f(x) \tag{1}$$

Next, we consider a Markov chain with the state space $\Phi = \{1,2,\dots,N\}$, with state transition diagram as shown in Fig. 1 and the states in Φ represents a concentration level of the drug. For any two states, $i, j \in \Phi$, if $f(i) > f(j)$, then it is indicated that the therapeutic performance of the drug at concentration level i is better than concentration j. We also assume that, in the Markov chain, the state $x(t)$ at any time t tends to change along the direction with greater probability to the next state $x(t+1)$ that makes the objective function $f(x(t+1))$ greater than $f(x(t))$. In this case, the state $x(t)$ will most likely approach the optimal state x^* as t goes to infinite. In other words, the steady-state probability of the optimal state x^* is largest.

Next, we will introduce two lemmas as below. The proofs of these two lemmas can be found in any books about stochastic process, including the one by Ross [14].

Lemma 1: If a homogeneous Markov chain with finite states is irreducible, then all the states are positive recurrent.

Lemma 2: For an irreducible aperiodic Markov chain, if all states are positive recurrent, that is,

$$\pi_j = \lim_{n\to\infty} P_{ij}^n > 0 \tag{2}$$

then $\{\pi_j, j = 0,1,2,\dots\}$ *is a stationary distribution and there exists no other stationary distribution.*

Reconsider the Markov chain as described above. From the state-transition diagram as shown in Fig.1, it is obvious that this is a random walk with two elastic walls. It is exactly an irreducible homogeneous aperiodic and positive recurrent Markov chain. By the two lemmas stated as above, this Markov chain has a unique stationary distribution. Therefore, through the above analysis, searching for the optimal drug concentration is equivalent to seeking the state which has the largest steady-state probability in the stationary distribution.

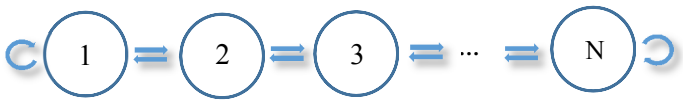

Fig. 1. The state-transition diagram of an irreducible homogeneous aperiodic and positive recurrent Markov chain.

C. Novel algorithm based on the Markov Chain

1) Step 1: Initialize the Markov Chain.

Without prior knowledge of drug response function, it is reasonable to assume that any drug concentration level $x \in \Phi$ has equal probability to become the optimal concentration. In other words, in the Markov chain, the optimal state x^* is a random discrete variable that is subject to the uniform distribution between 1 to N. Therefore, the transition probabilities between any two neighboring states are equal to 0.5 and the transition probability matrix can be written as below:

$$P = \begin{pmatrix} 0.5 & 0.5 & 0 & 0 & 0 & \cdots & 0 \\ 0.5 & 0 & 0.5 & 0 & 0 & \cdots & 0 \\ 0 & 0.5 & 0 & 0.5 & 0 & \cdots & 0 \\ & & & \cdots & & & \\ 0 & 0 & \cdots & 0 & 0.5 & 0 & 0.5 \\ 0 & 0 & 0 & 0 & \cdots & 0.5 & 0.5 \end{pmatrix} \tag{3}$$

Hence we can obtain the stationary distribution $\pi = (\pi_1, \pi_2, \dots, \pi_N) = (\frac{1}{N}, \frac{1}{N}, \dots, \frac{1}{N})$ from the stationary equation set

$$\begin{cases} \pi = \pi P \\ \sum_j \pi_j = 1 \end{cases} \tag{4}$$

and this is consistent with our expectation: the optimal state x^* is subject to a uniform distribution between 1 to N.

2) Step 2: Choose the appropriate experiment points.

Before searching for the optimal drug concentration level, a set of experiments at a set of properly selected drug combinations need to be carried out. The experiment points are composed of two sets E_A and E_B. Basically, points in the set E_A can select randomly and the way to choose points in E_A is not unique. In general, uniform selection in the space of drug combinations is an ideal option. Another way to select points in E_A using Fibonacci method might be good as well. Then let $E_B = \{y: y = x + 1, x \in E_A\}$ and the set of experiment points $E = E_A \cup E_B$. The difference between the drug responses of the two neighboring points x and $x + 1$ is denoted as ε, namely $\varepsilon = f(x) - f(x + 1)$, it is used to update the transition matrix of the Markov Chain.

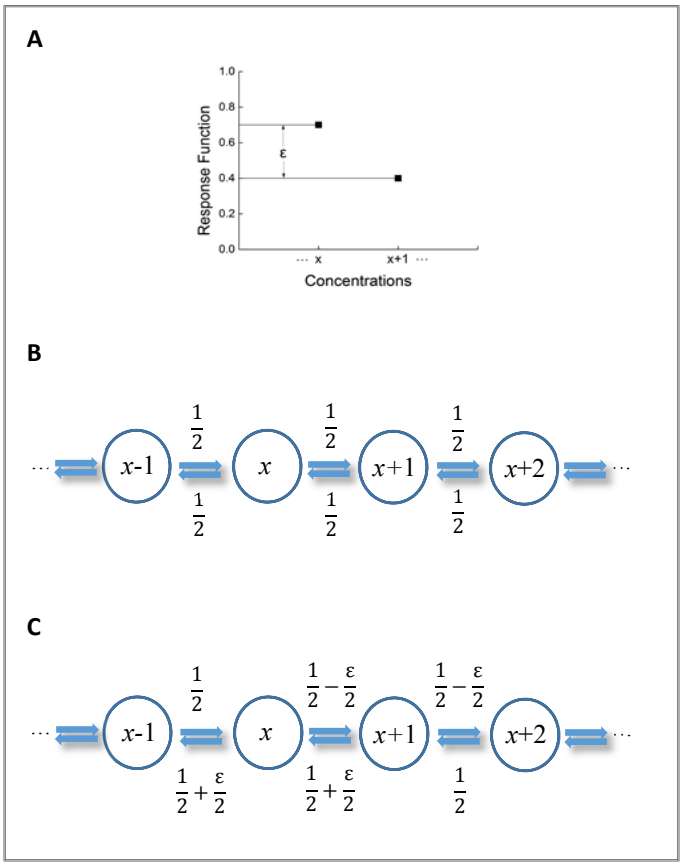

Fig. 2. The process of updating the transition probability matrix P. (A) the response function $f(x)$ of the experiment points' concentrations x and x+1; (B) initialize the Markov chain, for any two neighboring states, the transition probabilities between the two states are equal to 0.5; (C) update the transition probability of Markov chain after do experiments of points x and x+1.

3) Step 3: Update the transition probability matrix P.

Fig. 2 shows the process to update the probability transition matrix of the Markov chain by comparing the response function values at the points x and $x + 1$. The main idea is described as follows. If $\varepsilon < 0$, then the probability for the point x to become the optimal state x^* is equal to zero and the probability for $x + 1$ to become the optimal state becomes higher. Therefore the transition probability from x to $x + 1$ increases and that from $x + 1$ to x becomes smaller. On the other hand, if $\varepsilon > 0$, the transition probability from x to $x + 1$ decreases and that from $x + 1$ to x becomes larger. Accordingly we can update the transition probability matrix of the Markov chain.

In this study, we choose to update the values of transition probability linearly. In details, the transition probability from x to $x + 1$ is updated to $\frac{1}{2} - \frac{1}{2} * \varepsilon$ and the transition probability from $x + 1$ to x is updated to $\frac{1}{2} + \frac{1}{2} * \varepsilon$. Others transition probabilities are updated correspondingly, as shown in Fig. 2. Considering the extreme situation with $\varepsilon = 1$, which means that the state x has an excellent effect ($f(x) = 1, f(x + 1) = 0$), the state x can be chosen as the optimal state with probability 1. In this case, the transition probability from $x + 1$ to x is updated to the maximum value 1 and the state x is the optimal state.

According to the experimental result the transition probability matrix P is updated as below:

$$P = \begin{pmatrix} \frac{1}{2} & \frac{1}{2} & 0 & 0 & 0 & \cdots & 0 \\ \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 & \cdots & 0 \\ 0 & \frac{1}{2} & 0 & \frac{1}{2} & 0 & \cdots & 0 \\ & \cdots & \frac{1}{2} + \frac{\varepsilon}{2} & \cdots & \frac{1}{2} - \frac{\varepsilon}{2} & \cdots & \\ & & \cdots & \frac{1}{2} + \frac{\varepsilon}{2} & 0 & \frac{1}{2} - \frac{\varepsilon}{2} & \cdots \\ 0 & 0 & \cdots & 0 & \frac{1}{2} & 0 & \frac{1}{2} \\ 0 & 0 & 0 & 0 & \cdots & \frac{1}{2} & \frac{1}{2} \end{pmatrix} \tag{5}$$

4) Step 4: Predict the optimal state by the stationary equation set.

The optimal state can be predicted by computing the stationary distribution based on the updated transition probability matrix P. By solving the stationary equation set:

$$\begin{cases} \pi = \pi P \\ \sum_j \pi_j = 1 \end{cases} \tag{6}$$

the stationary distribution $\pi = (\pi_1, \pi_2, \dots, \pi_N)$ is updated. the stationary distribution obtained at k^{th} iteration is denoted as π^k.

5) Step 5: Determine stop or not.

The halt condition is not unique. For example, the halt condition can be set as the sequence of $\{\pi^k, k = 1,2, \dots\}$ converges, or as the iteration to update the transition probability matrix reaches a given number, etc. If the halt condition is satisfied, then the process to update the transition probability matrix is finished and the stationary distribution can be computed to find the optimal state x^*, or else the process keeps on and goes back to *Step 2*. ■

According to the algorithm stated above, in this study, we update the transition probability matrix P and predict the stationary distribution π^k until π^k is convergent. The state that has largest distribution value in π^k is selected as the optimal state, which represents the optimal drug concentration.

D. General cases: optimize combinatory drugs

For the general case of multiple drugs, the process to find the optimal combination of multiple drugs is similar to the case of a single drug. The difference is that a Markov chain in n-dimension space for the n combinatory drugs needs to be constructed. If each drug has m levels of concentrations, then the total drug concentration combinations is m^n and the state space for the Markov chain is $\Phi = \{1,2,\dots,m^n\}$. For instance, in the case of two drugs, we need to construct a Markov chain in two-dimensional network structure as shown in Fig. 3, in which each drug has 3 levels of concentrations and the Markov chain contains 9 states. It is easy to construct the transition probability matrix P correspondingly and to obtain the optimal combination using the Markov chain algorithms we mentioned above.

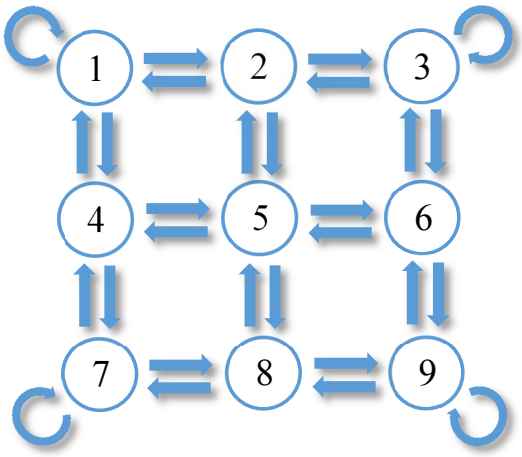

Fig. 3. Two-dimensional case: a Markov chain with 9 states in two-dimensional network structure.

III. Results and Discussion

A. Performance Comparison

We will compare, by the simulation, the performance of the proposed algorithm based on the Markov chain with the other two existing algorithms: the original Gur Game algorithm and the modified Gur Game algorithm proposed in [8]. Firstly, we will introduce the principles of these two algorithms briefly.

The basic idea for the Gur Game algorithm is to take a random walk in a finite state automaton (FSA) to find the optimal combination. The algorithm generates N random numbers $r_n \in [0,1]$ for $n = 1,\dots,N$. Each r_n is compared to the current drug response $f(x)$. If $f(x) < r_n$, the n^{th} drug is "penalized" and the concentration x_n is updated accordingly. Otherwise, the n^{th} drug is "rewarded" and its concentration is updated accordingly. Suppose the current concentration of the drug is $x_n = c_k$. If the current drug response $f(x)$ is smaller than the randomly generated number r_n, the algorithm penalizes the drug by switching the drug concentration to $x_n = c_{k-1}$. In the case that $f(x)$ exceeds r_n, the drug is rewarded and the algorithm updates the drug concentration to $x_n = c_{k+1}$. Note that the direction of state transition for rewarding (or penalizing) the current drug concentration is predetermined. According to this method, the current drug concentration x has a higher probability of being rewarded if $f(x)$ is high. Otherwise, the concentration x will be more likely to be penalized if $f(x)$ is low. In the original Gur Game algorithm, the rewarding state transition and the penalizing state transition are predetermined.

The modified Gur Game algorithm first evaluate the function

$$g(x, x_{prev}) = \frac{1}{2}\{1 + \alpha \cdot \max[f(x), f(x_{prev})]\} \qquad (7)$$

where $0 \le \alpha \le 1$ is a parameter that determines the randomness of the search algorithm. It is obvious that $g(x, x_{prev}) \ge 0.5$. The value of the function $g(x, x_{prev})$ is then compared to a uniformly distributed random number $r_n \in [0,1]$, based on which we decide how to make the next state transition. In the modified Gur Game algorithm, the rewarding and penalizing state transitions are determined by comparing the current drug response $f(x)$ to the previous drug response $f(x_{prev})$ [8], as illustrated in Fig. 4.

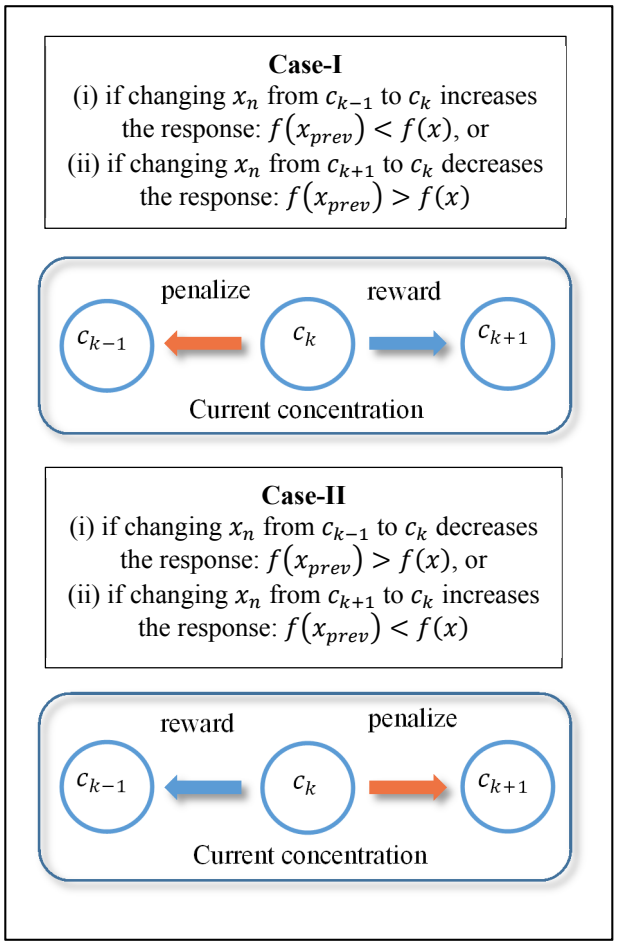

Fig. 4. The rules of modified Gur Game algorithm

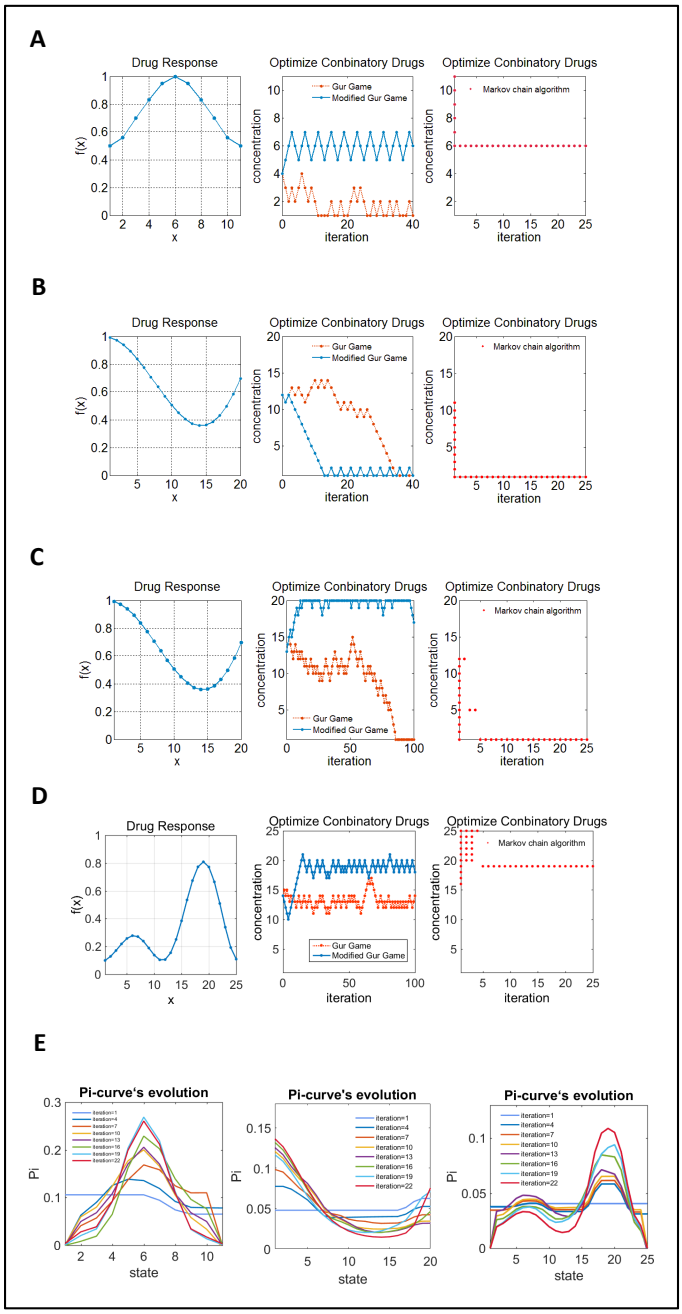

Fig. 5. The three drug response functions and the numerical simulations using three different algorithms. (A~D) left: drug response functions; middle: the original Gur Game algorithm and the modified Gur Game algorithm; right: the Markov chain-based algorithm. (E) The stationary distributions, corresponding to three drug response functions, converge to the patterns similar to the drug response functions as the transition probability matrices are updated.

Three single drug response functions, as shown in Fig. 5A-D, are selected for the performance comparison among the proposed algorithm based on the Markov chain and the algorithms based on the Gur Game rule. In Fig. 5B and Fig. 5C are the same drug response function to display non-robustness of the modified Gur Game algorithm. On the left column are the three drug response functions. In the middle column are the searching performance using the original Gur Game algorithm (red curve) and the modified Gur Game algorithm (blue curve), and on the right column is search performance using the Markov chain-based algorithm to find the optimal concentration. As we discussed previously, with the original Gur Game algorithm, it is not able to find the optimal state using when

$$f(x) \geq 0.5\,, \forall x \in \Phi \;\; or \;\; f(x) \leq 0.5\,, \forall x \in \Phi \qquad (8)$$

since the original Gur Game algorithm will always reward (or penalize) the current state with greater possibility whether it deserves or not for the reason that the values of objective function are always greater (or less) than the mathematical expectation of the random number r_n (Fig. 5A). The modified Gur Game algorithm could overcomes this defect but may take a large number of steps when the starting point is far from the optimal state, and this algorithm must pass all the states between the original starting point and the optimal point at least. In most cases, the number of concentrations is large so that the modified Gur Game algorithm cannot converge in a few steps. On the other hand, the modified Gur Game algorithm may stay in a suboptimal state sometimes (Fig. 5C). The common problem for the Gur Game-based algorithms is in that the state will oscillate instead of giving a single output even though the algorithm is convergent, which is caused by the shortcomings of the framework of Gur Game.

Unlike the Gur Game-based algorithms, the Markov chain-based algorithm could surmount the deficiencies mentioned above and predict the optimal state with a wonderful performance (right column of Fig. 5A~D). Generally speaking, choosing the experiment points uniformly in the state space may get more information to easily predict the global optimal state. The output of the Markov chain-based algorithm is the state that has the largest steady-state probability in the stationary distribution and the output unique usually. It is illustrated in right column of Fig. 5 that the Markov chain method gives the optimal state accurately and efficiently. Moreover, using the Gur Game-based algorithms, the drug concentration combinations at a certain iteration are predicted based on the previous drug response information, and then the experiments with predicted drug concentrations are carried out for the next iteration of prediction. Therefore, it usually takes a few hours or days to implement one iteration process and it may take more than a month to finish an optimization of combinatory drugs since most time is spent testing drug response in the experiments. However, the Markov chain-based algorithm allows us to simultaneously make all drug tests at the selected set of drug concentration combinations, i.e. parallel experiments, and then the optimization of combinatory drugs can be implemented based on the testing results. Comparing with the experimental time, the computational time is much less. Therefore, the Markov chain-based algorithm with parallel experiments could spend much less time than the Gur Game-based algorithm with serial experiments. For instance, if it takes 5~6 hours to test a drug concentration combination and 10 concentration combinations are needed to be examined in both parallel way and serial way. With the serial way more than two days will be spent finishing all test even though the experimenters are implemented continuously 24 hours per day. However, with the parallel way it just take 5~6 hours to finish all tests.

As shown in Fig.5 E, the stationary distributions $\pi = (\pi_1, \pi_2, \ldots, \pi_N)$ for three drug response functions gradually change as the transition probability matrices are updated. And it is obvious that the stationary distribution will converge to a pattern similar to the drug response, which illustrates the reason that the Markov chain-based algorithm is effective for optimizing combinatory drugs.

B. *Predicting the Optimal Combination of Multiple Drugs*

To further evaluate the performance of the Markov chain-based algorithm in the case of combinatory drugs, we use two different response functions of two combinatory drugs, as shown in Fig. 6. The first response function in Fig. 6A is the Peak function, which was obtained using the function *peaks()* in Matlab. The second function as shown in Fig. 6B was obtained by normalizing *the second De Jong function*. In Table 1 are the comparisons between the Markov chain-based algorithm and the other two Gur Game-based algorithms. The algorithm is effective if the optimized output *f(x,y)* exceeds a certain threshold (that is λ) or if the predicted output is among the top P% (even if the output is not necessarily close to the maximum value).We can obviously see that the Markov chain-based algorithm has a better performance than the other two stochastic algorithms, in terms of both reliability and efficiency.

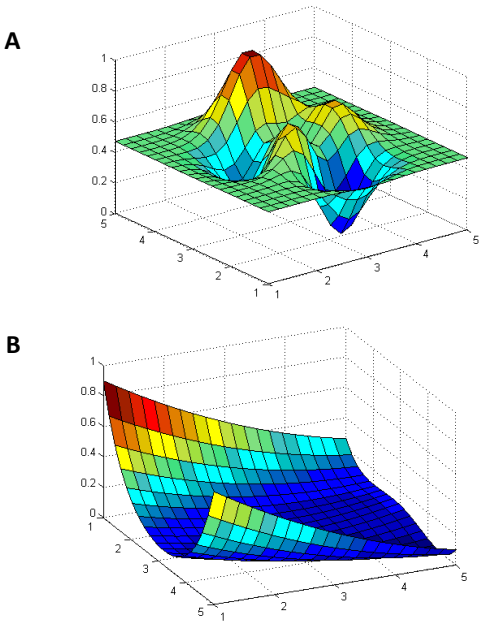

Fig. 6. Two response functions of combinatory drugs. (A) The peaks function in Matlab. (B) The 2nd De Jong function.

TABLE I. PERFORMANCE COMPARISON BETWEEN 3 ALGORITHMS

		Gur Game Algorithm		Modified Gur Game Algorithm		Markov Chain Algorithm	
		Success rate	*# of iterations*	*Success rate*	*# of iterations*	*Success rate*	*# of iterations*
A	λ=0.95	0.84	82.1	0.95	56.6	1.00	43.4
	P=5%	0.96	29.6	1.00	20.6	1.00	26.1
B	λ=0.95	0.09	43.1	1.00	56.7	1.00	16.3
	P=5%	0.12	28.6	1.00	49.5	1.00	19.9

IV. CONCLUSIONS

In this paper, a novel searching algorithm to solve the optimization of combinatory drugs is proposed from the point of view of "Markov chain". By comparing with the other two Gur Game-based algorithms, the Markov chain-based algorithm displays a superior performance in terms of both efficiency and accuracy.

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