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Synthetic Repurposing of Drugs in Hypertension: a Datamining Method Based on Association Rules and a Novel Discrete Algorithm

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Abstract

Background: Drug repurposing aims to detect new benefits of the existing drugs and to reduce the time and cost of drug development projects. Although synthetic repurposing of drugs may be more useful than single repurposing in terms of reducing toxicity and enhancing efficacy, the researchers have not taken it into account. To address the issue, a novel datamining method is introduced and applied to the repositioning of drugs in hypertension (HT). This disease is a complex one and needs to efficient treatment plans to cure it better.

Methods: A novel two-step data mining method, which is based on the If-Then association rules and a novel discrete optimization algorithm, is proposed and applied to the synthetic repurposing of drugs in HT. The required data are extracted from DruhBank, KEGG, and DrugR+ databases.

Results: The outcomes presented that the proposed method outperforms other state-of-the-art approaches in terms of different statistical criteria. Since different methods failed to discover the list for some datasets, our method could suggest a combination of drugs for all the datasets.

Conclusion: Due to using a minimum dosage of medicines, the synthetic method may revive some failed drug development projects and maybe a suitable plan for curing orphan and rare diseases. Also, to achieve better outcomes, it is essential to use efficient computational methods.

Keywords: Data mining; Drug repurposing; Hypertension; Optimization algorithm; Synthetic repurposing.

1- Introduction

Hypertension (HT) is a long-term medical condition in which blood circulates abnormally on the vessels. Based on the nature of the HT, the patients are divided in two categories, including (1):

i) The primary HT: genetic factors and lifestyles such as slat diet, smoke, alcohol, stress, overweight, etc. (2) have an important role in inducing the HT. More than 90% of the HT patients, mostly adults, are placed in this category.

ii) The secondary HT: due to other diseases such as chronic kidney diseases (3), the patients are infected with the HT. Less than 10% of patients, their HT may be reduced by treating the central illness (4), places in this class.

According to the world health organization, about 1.3 billion people around the world have HT, which is a remarkable number (5). Most of these patients are from low and middle-income countries (6) and need proper therapy plans with maximum efficacy, such as drug repurposing (7). For treating the disease, drug repurposing or drug repositioning, which may be a suitable option, incorporates some main advantages. First, it reduces the time and cost of HT drug development. Second, it may be useful in curing orphan and rare HT diseases, which developing new molecular entities for them is not affordable for drug companies. Third, it is possible to discover more practical applications of the existing drugs than their previous usages.

Besides to exploit drug repurposing benefits, synthetic repurposing, in which a combination of two or more drugs are prescribed instead of a specific drug, may lead to various advantages, including:

i) It may reduce the toxicity of medicines because minimum dosages of them are used (8). Hence, this concept can revive the drug development projects which have failed due to much amount of toxicity.

ii) It may enhance the efficacy of drugs and lead to better treatment plans. Finding a proper combination of drugs can show a synergic effect and control diseases better than single therapy. However, drug-drug adverse reactions are the main challenge that must be considered (9).

iii) It may open a new research branch in the drug repurposing field and develop the usages of drugs for a wide range of diseases (10). Meanwhile, pharmaceutical sciences can play a critical role in determining the dosage of drugs and their technical issues.

iv) The outcomes of the proposed method may also be used for combination therapy in which some other drugs can enhance the efficacy of a drug when they combined with it (11). The main difference between synthetic treatment and combination therapy is that the first one uses a synthetic of drugs instead of a given medication, whereas the second one combines one or more medications with a given prescription (12).

The study aims to introduce the synthetic repurposing of drugs as a useful tool for treating various diseases such as HT. For this purpose, a novel datamining method, which is based on our proposed algorithm, is presented. Our approach consists of two main parts. First, If-Then association rules are applied to a vast volume of data, and various information such as drug-target interactions, drug-drug adverse reactions, and drug-diseases data are extracted. Second, the proposed discrete algorithm (Trader) (13) is introduced and used for discovering synthetic lists that may be useful in managing HT.

2- Related works

From the computational perspective, this section investigates and categorizes literature works related to the repurposing of drugs into several groups, as follows:

i) Machine learning-based researches: these methods explore the existing data and try to discover the relationships between inputs and outputs (14). Overall, three types of machine learning methods such as supervised, semi-supervised, and unsupervised techniques have been used in drug discovery scope (15). Also, it has been shown that some modified and improved versions of the approaches such as deep neural networks can lead to better predictive models (16). Overfitting and lack of enough number of data are the main challenges in generating an appropriate predictive model(17, 18).

ii) Mathematical theory-based researches: based on numerical and experimental experiences, researchers formulate relationships between biological entities (19). For instance, different mathematic equations have been proposed for calculating the structural similarity between drugs (20, 21). Then, based on the similarity score, the role of analogous drugs is inspected for treating diseases (22). The idea is that the drugs, having similar structures (score), may be used instead of together. Even so, it has been reported that these methods are not applicable for most projects and some other criteria must be also considered (23).

iii) Graph and network theory-based researches: these approaches constitute a graph or a network that represents communications among the biological components (24). After that, graph algorithms are applied to the generated system (25, 26), and hidden

interactions are detected (27). Although these techniques confront minimal validation challenges and produce exciting results, they cannot be applied to most drug repurposing cases because biological elements follow the hypergraph theory (28, 29).

iv) Text mining-based researches: these methods delve a massive volume of raw data using different algorithms and discover desired data (30). K-means, KNN, association rules, and genetic algorithms are prevalent drug repositioning strategies in this field (31, 32). For acquiring proper outcomes, it is essential to organize data correctly and to exert state-of-the-algorithms. Our proposed approach, which employs association rules (If-Then) (33) and novel discrete algorithm (Trader), fits into this category of the related works.

v) Ensemble method-based researches: these approaches combine various techniques in various ways (34). By doing this, an efficient tool for predicting and discovering the hidden benefits of drugs can be generated (35). For example, some of the related works have mixed different aspects of the computational methods and have obtained a suitable predictive model (36, 37). From the biological point of view, it has been shown that simple techniques are sometimes better than complex ones (38). In other words, ensemble methods strongly incline to the existing data and are rapidly overfitted.

3- Materials and methods

For discovering drugs that may be useful in curing the HT, a two-step datamining method is proposed. In the first step, based on If-Then rules, it is determined which drugs can inhibit or

prevent the targets inducing HT. In the second step, the proposed discrete Trader optimization algorithm chooses an optimal subset of the candidate drugs whose combinations may be helpful to treat the HT. Fig. 1 presents the framework of the proposed method.

There are several steps in the first part of the proposed approach, as follows:

i) Obtain data: the data related to drugs and their different targets were acquired from DrugR+ (39), which is a relational database and has integrated DrugBank (40) and KEGG (41) databases. DrugR+ database provides an online tool that accepts a drug and suggests some potential drugs instead of it. Meanwhile, DrugR+ includes an advanced search section in which users can express their SQL queries and download the results immediately.

ii) Constitute the drug-disease (D-DI) matrix: based on the downloaded data, a binary matrix, named DDI and incorporated drugs-diseases relationships, is computed by Eq. (1).

$$\text{DDI(i,j)}=\begin{cases}1 if the i^{th} drug is used for treating the j^{th} disease \\ 0 else\end{cases} \quad (1)$$

Where i and j indicate a drug and a disease, respectively. The total number of drugs and diseases are 13,251 and 3,318, respectively.

iii) Constitute the drug-target (D-T) matrix: this matrix shows whether a drug affects a target or not. In the extracted data, there are four classes of drug-target effects, including (a) agonizing, (b) antagonizing, (c) inhibiting, and (d) inducing. The targets,

which their total numbers are 4893, consist of proteins and enzymes. DT matrix is valued by Eq. (2).

$$DT(i,j)=\begin{cases} IN\ if\ the\ i^{th}\ drug\ inhibits\ the\ j^{th}\ target \\ IND\ if\ the\ i^{th}\ drug\ induces\ the\ j^{th}\ target \\ AGO\ if\ the\ i^{th}\ drug\ agonists\ the\ j^{th}\ target \\ ANT\ if\ the\ i^{th}\ drug\ antagonists\ the\ j^{th}\ target \\ 0\ else \end{cases} \quad (2)$$

iv) Constitute the drug-drug adverse reaction (DDAR) matrix: Some drugs may interact with together, so it is possible that they neutralize their effects and may lead to critical problems in a body. Therefore, finding an adverse reaction-free subset of the existing drugs, which can be used for controlling HT, is a critical problem. For investigating the problem, a matrix, named DDAR, is formed by Eq. (3).

$$DDAR(i,j)=\begin{cases} 1\ if\ the\ i^{th}\ drug\ has\ adverse\ reaction\ with\ the\ j^{th}\ drug \\ 0\ else \end{cases} \quad (3)$$

v) Do mining: using the DT and DDI matrices, some other information, which will be used as input of the discrete Trader optimization algorithm, is extracted in several steps. In the first part, different targets related to blood pressure, along with their reasons (inhibiting, inducing, agonizing, and antagonizing), are determined and are placed in a set named HT_TARGETS. Eq. (4) presents the mentioned set:

$$HT\_TARGETS= [(T_1, R_1), \ldots, (T_n, R_n)] \quad (4)$$

Where n, T_i, and R_i are the total number of obtained targets, the i^{th} target, and the reason which leads to blood pressure disease, respectively.

Further, another set, named DRUGS, is created for holding drugs that directly interact with the HT_TARGETS collection and have an identical effect on the targets. For instance, *Angiotensin II* and *Candesartan* drugs interact with the *Type-1 angiotensin II receptor*. However, *Angiotensin II* affects the mentioned target as agonist whereas *Candesartan* affects it as an antagonist. Therefore, *Angiotensin II* is ignored because it does not have an identical role with the *Candesartan*.

In this study, an interaction between a drug such as D and a target such as T (protein (P) and enzyme (E)) is presented by "→". Besides, the action of D on T and the cause of blood pressure due to the defection of T are shown by F(D,T) and F(HT,T), respectively. In the second part, for all the existing drugs, the following rules are applied, and the candidate drugs are also added to the DRUGS set.

a) IF D → T && F(D,T) = F(HT,T) THEN

   D may be useful for controlling HT

b) IF E → P && F(E,P) = F(HT,P) THEN

   The drug, which interacts with E, may be useful for controlling HT

c) IF P → E && F(E,P) = F(HT,E) THEN

   The drug, which interacts with P, may be useful for controlling HT

d) IF P_1 → P_2 && F(P_1,P_2) = F(HT,P_2) THEN

   The drug, which interacts with P_1, may be useful for controlling HT

e) IF E_1 → E_2 && F(E_1,E_2) = F(HT,E_2) THEN

   The drug, which interacts with E_1, may be useful for controlling HT

In the second part of the proposed method, the discrete Trader optimization algorithm is applied to select optimal subsets of the obtained drugs, which may reduce the pressure of blood. For this purpose, there are several steps as follows:

i) Create the first population of candidate solutions (CSs): Trader algorithm begins with the randomly created of potential answers, which are presented by an array shown in Eq. (5).

$$CS= [V_1, V_2, \dots , V_m, G, Score] \quad (5)$$

Where V_i, m, G, and score are the i^{th} variable, the total number of variables, the group, and the score or fitness of the CS. Every variable shows a drug and gets 1 or 0 value for the selected and unselected drug, respectively.

ii) Calculate the score of the CSs: The CSs are answers to the problem, and their worthiness is different from each other. In this study, the score is calculated by Eq. (6).

$$Score = AT - \frac{\sum_{i=m} SE_i}{\sum_{i=1}^{m} v_i} \quad (6)$$

Where m, v_i, SE, and AT represent the length of a CS, the value of the i^{th} variable (0 or 1), the total number of side effects related to the i^{th} drug, and the total number of covered targets corresponded to HT, respectively.

iii) Grouping CSs: The total number of groups and the total number of traders are the same, and a trader shows a group. At the beginning of the algorithm, the total number of members in the groups is the same. In the next iterations, the total number of members in a group is calculated by Eq. (7).

$$TM_i = \text{round}\left(\frac{property_i}{\sum_{k=1}^{T} property_k} \times (C - M \times T)\right) \quad (7)$$

Where TM_i, C, and T present the total number of members in the i^{th} group, the total number of CSs, and the total number of traders or groups, respectively. M is a constant value (2) and guarantees that none of the groups are eliminated in the iterations of the algorithm's steps. Also, $property_i$ shows the property of the i^{th} trader and is calculated by Eq. (8).

$$property_i = \sum_{i=1}^{M} score(CS_i) \quad (8)$$

Where M and score show the total number of CSs in the i^{th} group and the score of corresponded CS, respectively. In other words, the property of a group is tantamount to the sum of its CSs' scores.

iv) Change the CSs: there are three operators, who change the master and slave CSs. These operators, named retailing, distributing, and importing-exporting, try to improve the CSs based on Eq. (9), Eq. (10), and Eq. (11), respectively. Using the retailing operator, the minimum number of changes are applied to a slave-CS. The

distributing operator gets some value from the best of the group (the master-CS) and, then, assigns them to a CS. While the distributing and retailing operators change slave-CSs, the importing-exporting operator leads to changes in the master-CSs. For all the operators, the changes are accepted provided that they improve the value of a CS's score.

$$\sum_{i=1}^{R}(CS_{slave}(K) = |(CS_{slave}(K) - 1)|) \qquad (9)$$

Where K and R are two random integer values in [1, length(CS)] and in [1, length(CS)/10], respectively.

$$\sum_{i=1}^{R}\left(CS_{slave}(K) = CS_{master}(K)\right) \qquad (10)$$

Where K and R are two random integer values in [1, length(CS)].

$$\sum_{i=1}^{R}\left(CS_{master_j}(K) = CS_{master_m}(K)\right) \qquad (11)$$

Where j and m are the importer and exporter CSs, respectively. Also, the values of K and R are computed in the same way calculated in Eq. (9).

Here is Fig. 2, which illustrates how the mentioned operators are applied to the CSs.

4- Results

The proposed method for the synthetic repurposing of drugs was implemented in MATLAB programming language and was compared with four state-of-the-art algorithms including discrete symbiotic optimization search (DSOS) (42), forest optimization algorithm (FOA) (43), world competitive contests algorithm (WCC) (44), and cuckoo optimization (CUK) algorithm (45). Next, they were applied to the generated datasets which have been described in Table 1. The selected drugs are used for controlling HT and belong to the different groups of treatment methods. For every drug, three main information exist, including i) the total number of a drug's targets consisting of main targets and side effects, ii) the total number of a drug's targets which are effective in controlling hypertension, and (iii) the total number of drugs which have a common target with one of the main targets of the specified drug. For instance, Nicardipine interacts with 15 targets from which 4 targets play a critical role in curing hypertension, and the remaining 11 targets not (side effects). Also, 40 drugs have at least interaction with the main targets of Nicardipine. The goal is to determine an optimal subset of drugs, which can control hypertension instead of the specified drug such as Nicardipine.

The obtained outcomes of applying the algorithms to the datasets have been divided into two categories, as follows:

i) In the first class of evaluations, the performance of the algorithms is examined in terms of convergence, stability, and some statistical criteria such as P-value, standard deviation (STD), etc. Due to the stochastic operations of the optimization algorithms, they generate various results in their different runs. Hence the algorithms were

individually executed 50 times, and then, their data were analyzed. For all the algorithms, an identical circumstance was considered, and they invoked the same number of the score function. Fig. 3 represents the convergence of the algorithms on the generated datasets, which relate to the selected drugs. Horizontal and vertical axes show the iteration number and the best-obtained score, respectively. When the size of the problem or candidate drugs is small, most of the algorithms can choose the best possible subset of medicines for curing HT. However, their performances and convergences reduce when the total number of candidate drugs rises, and they may not acquire the best answer for the synthetic repurposing of drugs. For instance, the FOA algorithm has acquired the best solution to the Trandolapril dataset. Still, it does not earn the best synthetic of medicines for the remaining datasets and falls into local optima solutions.

The principle of the meta-heuristic algorithms is approximately the same. For example, these algorithms generate some random potential answers to a problem and, then, try to improve them based on some random-based operations (46). Therefore, they must be executed at least 30 times, and their performances are evaluated based on the produced data (47). An algorithm, whose results in disparate runs are close together, is more stable than others. Likewise, the generated outcomes must be better than others' data. Fig. 4 demonstrate the algorithms' stability properties on the created datasets in 50 distinct executions.

Horizontal and vertical axes indicate the execution number and the score of the best CS, respectively. For the Trandolapril dataset, all the algorithms have obtained the

best possible answer in all the executions, and the results overlap. With rising the candidate drugs, the stability of the algorithms differs from together. Overall, the stability power of the algorithms can be considered as Trader, WCC, DSOS, FOA, and CUK, respectively.

To analyze the functionality of the algorithms accurately, Table 2, relating to the results of the algorithms on the generated datasets in 50 distinct executions, has been provided. In addition to the name of datasets and algorithms, Table 2 consists of several criteria, including (i) the worst outcomes of the algorithms, (ii) the best outcomes of the algorithms, (iii) the average value of the results, (iv) The p-value, which states how much the results of the algorithms is produced by chance, (v) standard deviation (STD) of the results, and (vi) the confidence interval (CI), which indicates a range in which the outcomes of the algorithms is expected to acquire. For the Trandolapril dataset, the performance of all the algorithms is the same. For the Atenolol and Nicardipine datasets, the best results of the Trader and WCC algorithms are alike. For the Felodipine dataset, the best-obtained score of the WCC algorithms is better than other algorithms, but it is close to the best-acquired outcome of the Trader algorithm. For all the remaining datasets, the Trader algorithm (proposed algorithm) has a proper functionality than others have.

Here is Table 3, which is an average of the data of Table 2 and compares the algorithms overall. This Table demonstrates that the proposed method is the more suitable option for the synthetic repositioning of drugs than others.

In another comparison of the algorithms, their performance was examined based on the p-value (48). For this purpose, the results of the proposed algorithm (Trader) were considered as a test base and were compared against the others' outcomes (Table 4). Since the p-value of Table 2 states how much the results of the algorithms are random, the p-value of Table 4 demonstrates whether the performance of the proposed algorithm is equal to others or is efficient than them. The considered hypothesis between the proposed algorithm and another algorithm such as A are as follows:

H_0: The performance of the proposed algorithm and A is the same.

H_1: The performance of the proposed algorithm is efficient than A.

If the p-value is less than 0.05, H_0 is rejected and H_1 is accepted. In contrast, H_0 is accepted and H_1 is rejected.

ii) In the second part of the outcomes, the results of the algorithm are discussed from the drug synthetic repurposing aspect. For every drug, Table 5 demonstrates a list of drugs that may be used instead of a given drug.

Trandolapril is a small molecule, which inhibits angiotensin-converting enzyme (ACE) and is used for treating moderate HT (49). This medication only interacts with the ACE, who is responsible for controlling the rate of fluids in a body and, therefore, manages the HT. As table 5 indicates, all the algorithms have found a drug with a minimum number of side effects for using instead of Trandolapril.

Atenolol is a beta-blocker, which is used for curing abnormal heart rhythms and also interacts with the ACE (50). Like the Trandolapril, all the algorithms have chosen a drug instead of Atenolol. However, the proposed drugs have a different number of side effects. From this point of view, Trader, WCC, and DSOS, which have found substitutions without side effects, are better than FOA and CUK. In addition to the ACE, Nebivolol and Alprenolol affect some other targets.

Carteolol acts against the beta-2 adrenergic and partially agonists beta-1 adrenergic receptors (51). As a result, the pressure of the blood is reduced, and this drug may be an option for treating the HT. Although all the algorithms propose some lists, the size of lists and their costs differ from each other. Based on the score function, the Trader and WCC algorithms have obtained a proper outcome than others.

Nicardipine is a calcium channel blocker and leads to controlling blood pressure (52). For this drug, CUK and FOA cannot obtain some candidates to replace with it. Since the WCC and DSOS have acquired only a synthetic list instead of Nicardipine, the Trader yields two lists for it. Considering the score function, all the lists have an identical value and maybe a suitable choice for treating the HT.

By inhibiting the calcium channels, Felodipine controls the pressure of blood and maybe a proper option for curing mild and moderate HT (53). For the HT treatment instead of Felodipine, the algorithms have mined a pair of medications, which all of them include Pinaverium. Nevertheless, the list, provided by Trader, has the best value of score relative to the lists resulted from the others.

Nifedipine and Nisoldipine are drugs that slow the penetration of calcium into heart cells and vessel walls (54). Thus, the heart can efficiently pump and ream blood vessels. Except for the Trader, other algorithms fail to discover candidates who may be used instead of them. The Trader algorithm suggests one and two possible lists for the treating HT instead of Nifedipine and Nisoldipine, respectively.

Doxazosin acts against Alpha-1A, Alpha-1B, and Alpha-1D adrenergic receptors and smooths the growth of muscle cells (55). Since CUK and FOA are not successful in detecting substitution drugs instead of Doxazosin, Trader, WCC, and DSOS have discovered a single-member list. Based on the worthiness of the provided lists, the functionality of the algorithms can be sorted as Trader, WCC, and DSOS, respectively.

Prazosin belongs to a group of drugs that operate against Alpha-1A, Alpha-1B, and Alpha-1D adrenergic receptors. In comparison among the outcomes of the algorithms, it is shown that the Trader has acquired three different lists for controlling the HT instead of Prazosin, whereas other algorithms have obtained a two-member list. Also, from the score value viewpoint, the lists, which have been provided by the Trader, are more suitable than the lists provided by the others.

Considering the obtained results, it can be concluded that the Trader algorithm is efficient than other state-of-the-art ones and yields better synthetic drug lists for treating the HT instead of the given drugs. Table 6 compares the outcomes of the Trader for the selected drugs with details. This table also includes information of similarity between drugs that are calculated by Eq. (12) (56):

$$\text{Similarity } (D_i, D_j) = \frac{\sum_{r=1}^{n}\left(w|r \times C_{i,r} \times C_{j,r}\right)}{\sum_{r=1}^{n}\left(\sqrt{w_{r\times}C_{i,r}}\sqrt{w_{r\times}C_{j,r}}\right)} \qquad (12)$$

Where D_i, D_j, n, $C_{i,r}$, and $C_{j,r}$ are the i^{th} drug, the j^{th} drug, the total number of chemical components, the total number of the r^{th} chemical component in the i^{th}, and the total number of the r^{th} chemical component in the j^{th} chemical component, respectively. Also, w_r, which is calculated by Eq. (13), is the weight of the r^{th} chemical component.

$$w_r = \frac{min(d_r,1)\times min\left(C_{i,r},C_{j,r}\right)}{max\left(C_{i,r},C_{j,r}\right)+eps} \qquad (13)$$

Where d_r shows the data frequency of the r^{th} chemical component.

5- Discussion

To discover hidden applications of the existing drugs, a novel synthetic method based on the novel discrete Trader optimization algorithm was introduced. The introduced method may reduce the toxicity of drugs and enhance the efficacy of them in curing diseases. To investigate the applicability of the proposed method, it was applied to nine hypertension-related datasets, and the results were then described. The obtained outcomes can be discussed in two aspects. From the first viewpoint, we showed that state-of-the-art algorithms yield better various outcomes than others. The average value of score and the confidence interval of the Trader are -7.79 and [-9.05 -6.52], respectively, which are remarkably better than the results of other

algorithms. Besides, the proposed algorithm can detect some lists for all the datasets, whereas others fail. For example, except for the Trader, the other algorithms cannot explore candidates for the Nifedipine and Nisoldipine datasets. From the second viewpoint, the outcomes are discussed from the application of selected drugs in hypertension treatment. These results show some important findings. First, although the synthetic replacement of drugs may not exist for all the drugs, the proposed method can find some proper single substitutions for them. For instance, Atenolol interacts with two targets (57), one of which is responsible for the HT, and the remaining one is a side effect. Instead of Atenolol, the proposed approach suggests Esmolol which belongs to a family of beta-blocker drugs and does not have any side effects (58). Also, the mentioned drugs may be combined with their substitutions in the lower dosages. For example, it has been reported that a combination of Trandolapril and Cilazapril can show better efficacy in controlling the HT (59). Second, the proposed approach can introduce novel applications of some drugs. For instance, Pinaverium is a first-line option for curing bowl dysfunctionality and operates as an inhibitor and antagonist of the voltage-dependent calcium channel protein (60). Although the main application of Pinaverium is to cure gastrointestinal disorders and is used in more than 60 countries, the FDA has not approved it. Our method suggests that Pinaverium may have an application in HT and indicates that the synthetic repurposing of drugs may be the best option for reviving drug discovery projects. Especially, the introduced approach may revivify the projects which had failed due to the dosage of drugs (61). Besides, our method may be a suitable therapy choice for treating orphans or diseases, in which developing an efficient drug is not affordable for drug companies because of the huge volume of cost and time (62). Another discovered medication for managing the HT is Dapiprazole which

is an alpha-blocker agent. After investigating the eye, it is possible that the pupil of it dilates (63). To reverse the mydriasis effect, doctors prescribe Dapiprazol, which helps to reduce the size of the eye's pupil. Although different studies have reported many undesired side effects of Dapiprazole and other drugs such as Pinaverium (64), the proposed approach employs these drugs in an appropriate manner. To this end, the minimum dosages of the drugs are used, so the undesired effects of them are also eliminated or decreased (65). Further, a combination of the drugs may show a synergic effect in curing the HT because of having common targets (66). In this field, although some drug-drug adverse reactions have been determined, most of them are not specified.

6- Conclusion

A novel discrete algorithm, named Trader, was introduced for the synthetic repurposing of drugs. This concept can resume most of failed drug discovery projects and maybe the most suitable option for treating orphan and rare diseases. The proposed approach considers various aspects of the synthetic repositioning of medications such as the mechanism of action of drugs on targets, drug-drug adverse reactions, and the total number of side effects. Based on the acquired outcomes, it can be concluded that the-state-of-the-art algorithms yield better results than others and show better functionality than them. Furthermore, the obtained results

validate the functionality of the proposed method and introduce several synthetic repurposing lists for reducing hypertension.

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Abbreviations

ACE: Angiotensin-Converting Enzyme

ATE: Atenolol

CAR: Carteolol

CI: Confidence Interval

CS: Candidate Solution

CUK: cuckoo optimization

D-DI: Drug-Disease

D-T: Drug-Target

DDR: drug-drug adverse reaction

DOX: Doxazosin

DSOS: discrete symbiotic optimization search

FEL: Felodipine

FOA: forest optimization algorithm

HT: Hypertension

NIC: Nicardipine

NIF: Nifedipine

NIS: Nisoldipine

PAR Prazosin

STD: Standard Deviation

TNC: Total number of candidates

TNMT: total number of main targets

TNT: total number of targets

TRA: Trandolapril

WCC: world competitive contests

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Authors' contribution

Yosef Masoudi-Sobhanzadeh: Conceptualization, implementation, formal analysis, investigation, writing, editing, and revising the manuscript. **Ali Masoudi-Nejad**:

Conceptualization, Supervision, Project administration, writing, editing, and revising the manuscript. All authors have read and approved the manuscript.

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https://github.com/LBBSoft/Trader

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

Figures

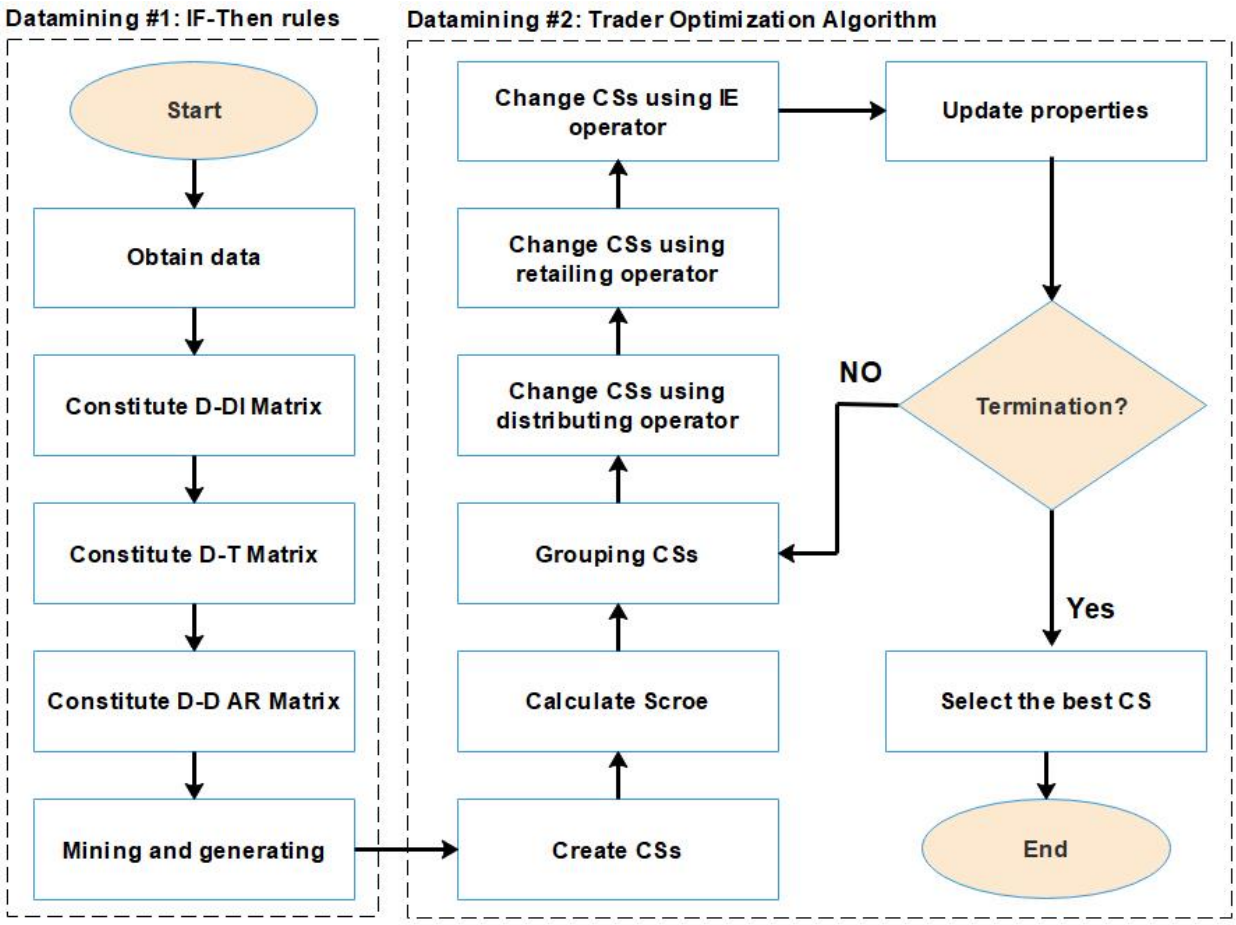


Fig. 1: The framework of the proposed method. In the first step, the desired data are obtained from DrugR+ database. Next, drug-disease (D-DI), drug-target (D-T), and drug-drug-adverse reaction (D-D AR) matrices are constituted. Based on If-then rules, the drugs, which can affect targets related to HT, are acquired. In the second step, the proposed optimization algorithm (Trader) is applied to select a combination of drugs for the repurposing in HT.

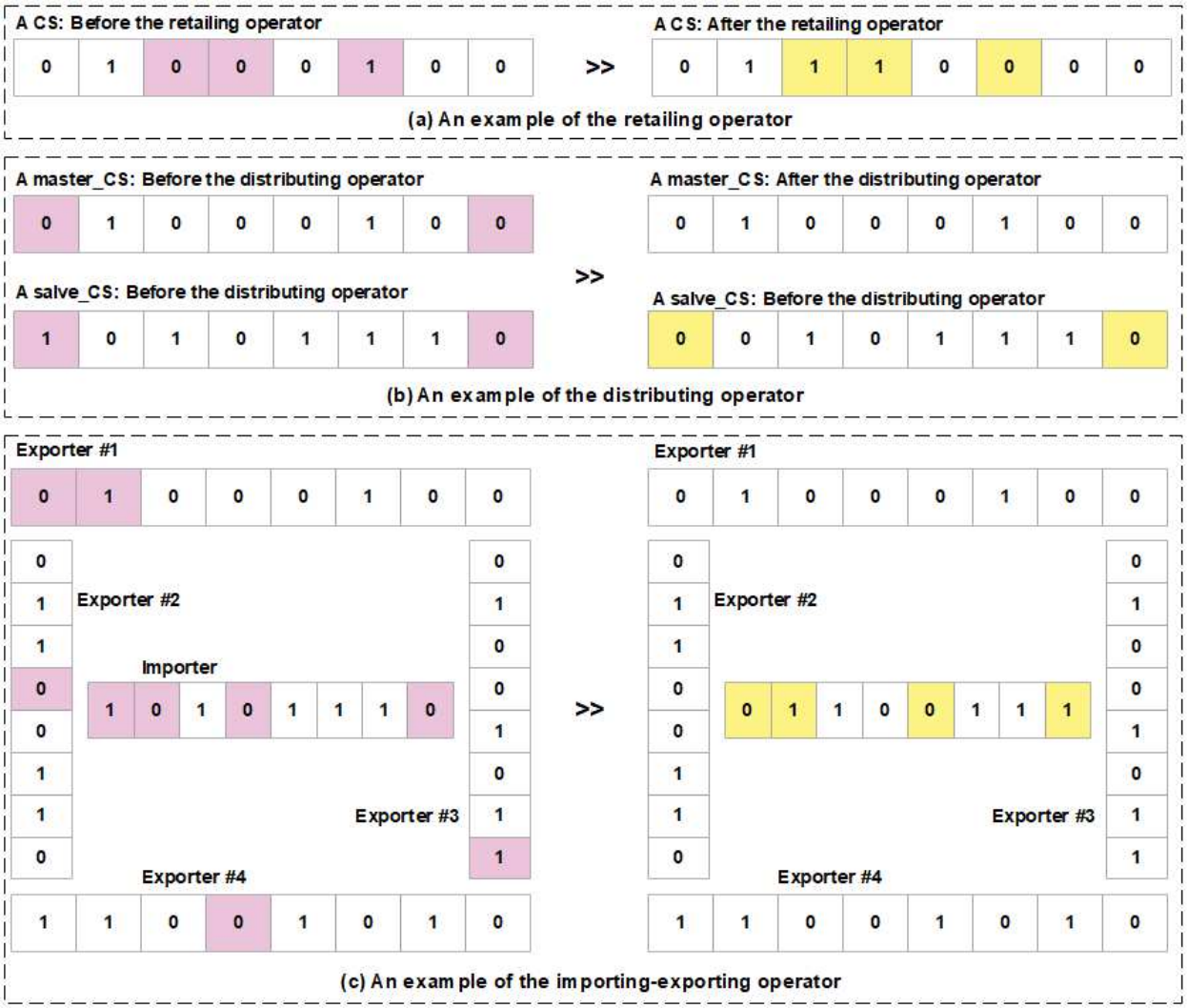


Fig. 2: Trader's operators. (a) An example of the retailing operator: three points have been randomly chosen, and, then, their values have been updated by Eq. (9). This operator is only applied to slave_CSs. (b) An instance of the distributing operator: The master_CS selects two values from himself and distributes them into the slave_CS. (c) An example of the importing-exporting operator: The exporter CSs select some of their values and send them toward the importer CS. After applying the operators, the score function is called. Provided that the new score is better than the previous one, the changes are accepted. In contrast, the changes are ignored, the previous values are retrieved from the memory.

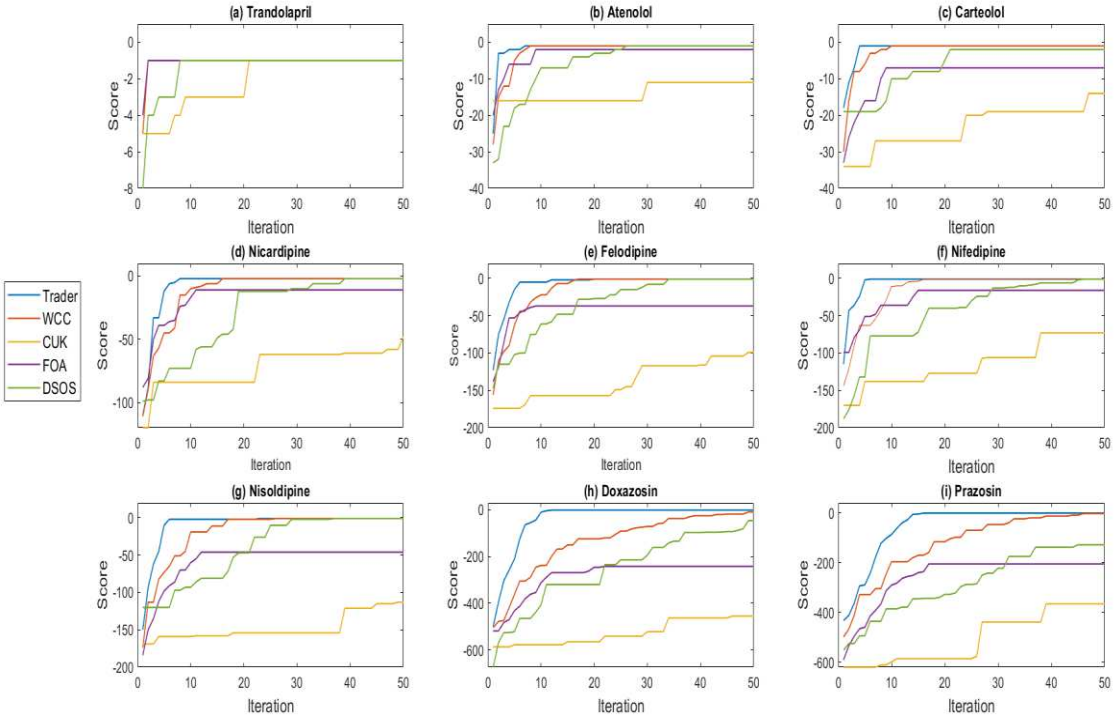


Fig. 3: The convergence behavior of the algorithms on the generated datasets. (a) The convergence of the algorithms on the Trandolapril dataset. (b) The convergence of the algorithms on the Atenolol dataset. (c) The convergence of the algorithms on the Carteolol dataset. (d) The convergence of the algorithms on the Nicardipine dataset. (e) The convergence of the algorithms on the Felodipine dataset. (f) The convergence of the algorithms on the Nifedipine dataset. (g) The convergence of the algorithms on the Nisoldipine dataset. (h) The convergence of the algorithms on the Doxazosin dataset. (i) The convergence of the algorithms on the Prazosin dataset. For the datasets with the small sizes, the performance of the algorithms is almost the same. With enhancing the total number of candidate drugs (the size of the problem), the functionality of the algorithms differs from each other. From the proper convergence behavior, the algorithms can be considered as Trader, WCC, DSOS, FOA, and CUK, respectively.

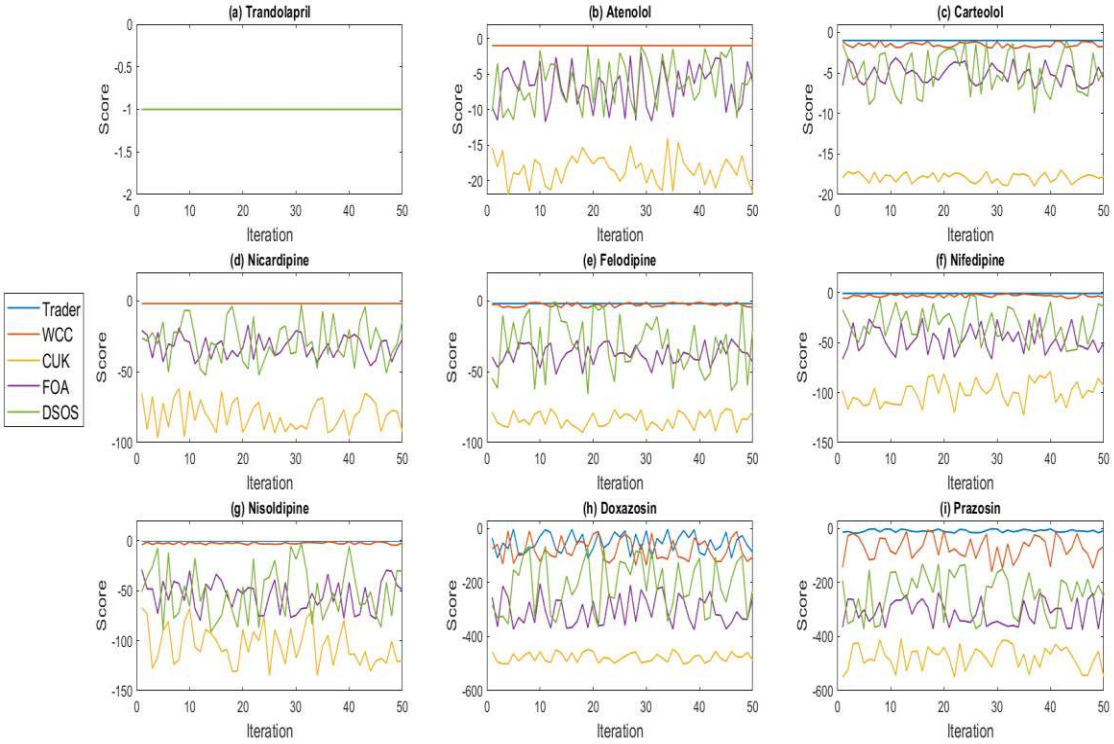
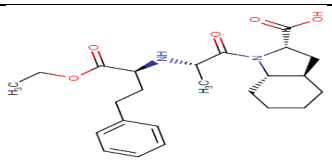
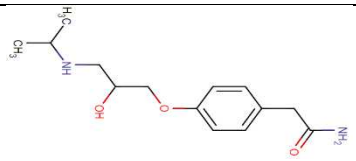
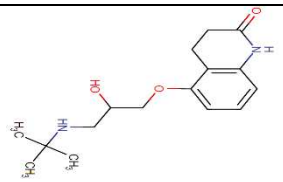
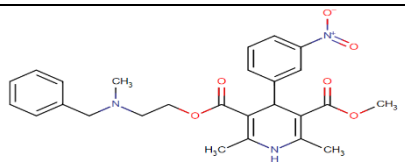
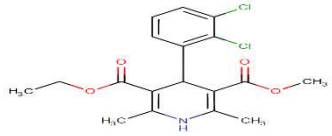
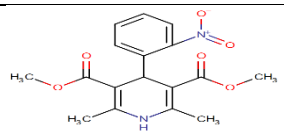
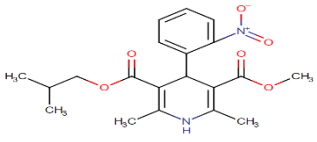
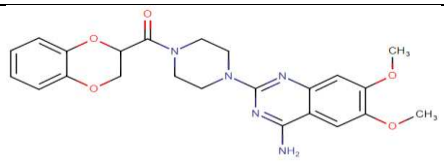


Fig. 4: The stability behavior of the algorithms on the generated dataset. (a) The stability of the algorithms on the Trandolapril dataset. (b) The stability of the algorithms on the Atenolol dataset. (c) The stability of the algorithms on the Carteolol dataset. (d) The stability of the algorithms on the Nicardipine dataset. (e) The stability of the algorithms on the Felodipine dataset. (f) The stability of the algorithms on the Nifedipine dataset. (g) The stability of the algorithms on the Nisoldipine dataset. (h) The stability of the algorithms on the Doxazosin dataset. (i) The stability of the algorithms on the Prazosin dataset. Except for the Trandolapril and Nicardipine datasets, the Trader algorithm (proposed algorithm) is remarkably more stable than others and leads to better outcomes. Since the performance of other algorithms reduces with raising the total number of candidate drugs, the performance of the introduced algorithm (Trader) is better than others.

Tables

Table 1. The properties of the generated datasets

DrugBank Id	Drug name	Abbr	Chemical structure	TNT	TNMT	TNC
DB00519	Trandolapril	TRA		1	1	16
DB00335	Atenolol	ATE		2	1	26
DB00521	Carteolol	CAR		2	2	28
DB00622	Nicardipine	NIC		15	4	40
DB01023	Felodipine	FEL		13	5	50
DB01115	Nifedipine	NIF		8	5	50
DB00401	Nisoldipine	NIS		5	5	50
DB00590	Doxazosin	DOX		6	3	112

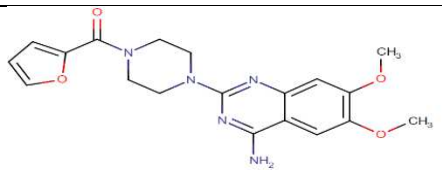
DB00457	Prazosin	PRA		6	3	112
TNT: total number of targets; TNMT: total number of main targets; TNC: Total number of candidates.						

Table 2. A comparison of the algorithms' performance on the generated datasets

Dataset	Algorithm	Worst	Best	Average	STD	P-value	Low of CI	High of CI
TRA	Trader	-1.00	-1.00	-1.00	0.00	0	-1.00	-1.00
	WCC	-1.00	-1.00	-1.00	0.00	0	-1.00	-1.00
	CUK	-1.00	-1.00	-1.00	0.00	0	-1.00	-1.00
	FOA	-1.00	-1.00	-1.00	0.00	0	-1.00	-1.00
	DSOS	-1.00	-1.00	-1.00	0.00	0	-1.00	-1.00
ATE	Trader	-1.00	-1.00	-1.00	0.00	0	-1.00	-1.00
	WCC	-1.00	-1.00	-1.00	0.00	0	-1.00	-1.00
	CUK	-21.93	-14.03	-18.40	1.98	2.00E-49	-18.96	-17.83
	FOA	-11.72	-2.01	-6.75	3.02	7.44E-21	-7.61	-5.89
	DSOS	-11.44	-1.09	-6.20	3.37	1.61E-17	-7.16	-5.24
CAR	Trader	-1.00	-1.00	-1.00	0.00	0	-1.00	-1.00
	WCC	-1.99	-1.02	-1.55	0.29	1.40E-37	-1.63	-1.47
	CUK	-18.97	-17.00	-17.90	0.54	1.49E-76	-18.05	-17.74
	FOA	-6.98	-3.15	-5.18	1.16	3.31E-34	-5.51	-4.85
	DSOS	-9.99	-1.04	-4.90	2.63	9.86E-18	-5.65	-4.15
NIC	Trader	-2.00	-2.00	-2.00	0.00	0	-2.00	-2.00
	WCC	-2.00	-2.00	-2.00	0.00	0	-2.00	-2.00
	CUK	-96.80	-61.69	-80.69	10.44	1.39E-45	-83.66	-77.73
	FOA	-45.91	-17.13	-32.25	7.71	6.68E-33	-34.44	-30.05
	DSOS	-52.49	-2.20	-28.40	14.57	1.72E-18	-32.54	-24.26
FEL	Trader	-2.00	-2.00	-2.00	0.00	0	-2.00	-2.00

	WCC	-4.99	-1.06	-2.92	1.32	1.17E-20	-3.30	-2.54
	CUK	-93.19	-76.13	-83.90	5.23	5.30E-61	-85.39	-82.42
	FOA	-51.84	-27.04	-37.57	6.79	1.25E-38	-39.50	-35.64
	DSOS	-65.78	-1.07	-31.28	20.26	1.01E-14	-37.04	-25.53
NIF	Trader	-1.00	-1.00	-1.00	0.00	0	-1.00	-1.00
	WCC	-5.90	-1.02	-3.42	1.48	1.60E-21	-3.84	-3.00
	CUK	-122.51	-78.98	-99.80	11.72	1.32E-47	-103.13	-96.46
	FOA	-67.15	-24.92	-47.31	12.75	1.63E-30	-50.93	-43.69
	DSOS	-58.92	-2.48	-31.63	15.91	8.08E-19	-36.15	-27.11
NIS	Trader	-1.00	-1.00	-1.00	0.58	0	-1.00	-1.00
	WCC	-4.68	-1.01	-2.81	1.06	5.62E-24	-3.11	-2.51
	CUK	-134.77	-67.15	-104.76	19.11	2.00E-38	-110.19	-99.33
	FOA	-79.83	-29.24	-54.61	15.54	1.96E-29	-59.02	-50.19
	DSOS	-91.12	-3.16	-51.46	26.04	1.02E-18	-58.86	-44.06
DOX	Trader	-109.49	-2.19	-52.34	35.19	3.66E-14	-62.35	-42.34
	WCC	-136.29	-8.11	-78.53	40.19	1.59E-18	-89.95	-67.11
	CUK	-500.91	-445.43	-476.60	17.31	1.90E-72	-481.52	-471.68
	FOA	-374.17	-203.50	-302.06	54.84	1.58E-38	-317.64	-286.47
	DSOS	-365.21	-65.66	-207.26	95.75	2.67E-20	-234.47	-180.04
PRA	Trader	-16.93	-1.03	-8.74	4.90	5.34E-17	-10.13	-7.35
	WCC	-160.25	-5.99	-70.80	42.14	4.89E-16	-82.78	-58.82
	CUK	-550.57	-407.07	-476.59	42.81	2.97E-53	-488.76	-464.42
	FOA	-374.62	-236.38	-310.26	46.38	1.48E-42	-323.44	-297.08
	DSOS	-371.64	-130.85	-242.03	77.59	4.26E-27	-264.08	-219.98

STD: standard deviation; CI: confidence interval; TRA: Trandolapril; ATE: Atenolol; CAR: Carteolol; NIC: Nicardipine; FEL: Felodipine; NIF: Nifedipine; NIS: Nisoldipine; DOX: Doxazosin; PAR Prazosin; WCC: world competitive contest algorithm; CUK: cuckoo; FOA: forest optimization algorithm; DSOS: discrete symbiotic optimization search.

Table 3. A comprehensive comparison of the algorithms' performance on the generated datasets

Dataset	Algorithm	Worst	Best	average	STD	P-value	Low of CI	High of CI
ALL	Trader	-15.05	-1.36	-7.79	4.45	4.07E-35	-9.05	-6.52
	WCC	-35.34	-2.47	-18.23	9.61	5.45E-37	-20.96	-15.49
	CUK	-171.19	-129.83	-151.07	12.13	2.22E-39	-154.52	-147.62
	FOA	-112.58	-60.48	-88.55	16.46	8.26E-42	-93.23	-83.87
	DSOS	-114.18	-23.17	-67.13	28.46	1.12E-35	-75.22	-59.04

STD: standard deviation; CI: confidence interval; WCC: world competitive contest algorithm; CUK: cuckoo; FOA: forest optimization algorithm; DSOS: discrete symbiotic optimization search.

Table 4. The P-value of the algorithms on the generated datasets based on the results of the Trader algorithm (proposed algorithm) as a test base

Algorithm	TRA	ATE	CAR	NIC	FEL	NIF	NIS	DOX	PRA
WCC	1.00	1.00	9.72e-18	0.01	1.00e-05	1.17e-15	2.77e-16	3.84e-7	1.12e-13
CUK	1.00	3.00e-48	2.49e-75	4.66e-45	1.72e-60	2.14e-47	3.15e-38	4.08e-51	1.51e-52
FOA	1.00	4.50e-18	6.67e-30	1.29e-31	1.68e-37	4.33e-30	4.54e-29	3.53e-30	6.92e-42
DSOS	1.00	1.01e-14	3.99e-14	2.87e-17	9.73e-14	2.84e-18	2.19e-18	3.45e-14	1.44e-26

TRA: Trandolapril; ATE: Atenolol; CAR: Carteolol; NIC: Nicardipine; FEL: Felodipine; NIF: Nifedipine; NIS: Nisoldipine; DOX: Doxazosin; PAR Prazosin; WCC: world competitive contest algorithm; CUK: cuckoo; FOA: forest optimization algorithm; DSOS: discrete symbiotic optimization search.

Table 5. The synthetic repurposing of drugs for the HT

	The selected drugs by the algorithms				
HT drug	Trader	WCC	CUK	FOA	DSOS
Trandolapril	Cilazapril	Enalapril	Fosinopril	Fosinopril	Quinapril
Atenolol	Esmolol	Esmolol	Alprenolol	Nebivolol	Practolol
Carteolol	(Xamoterol+Nebivolol)	(Xamoterol+Nebivolol)	Penbutolol	Penbutolol	Penbutolol
Nicardipine	(Cyclandelate+Nisoldipine), (Drotaverine+Nisoldipine)	(Drotaverine+Nisoldipine)	---	---	(Drotaverine+Nisoldipine)
Felodipine	(Pinaverium+ Nisoldipine)	(Pinaverium+Nilvadipine)	(Pinaverium+Mibefradil)	(Pinaverium+Nifedipine)	(Pinaverium+Nilvadipine)
Nifedipine	(Pinaverium + Nisoldipine)	---	---	---	---
Nisoldipine	(Pinaverium+Isradipine), (Pinaverium+Drotaverine+Nilvadipine)	---	---	---	---
Doxazosin	(Nicergoline)	(Droperidol)	---	---	(Dapiprazole)
Prazosin	(Dapiprazole), (Nicergoline+Tamsulosin), (Nicergoline+Periciazine+Dapiprazole)	(Alfuzosin+Flupentixol)	(Alfuzosin+Flupentixol)	(Alfuzosin+Phentolamine)	(Alfuzosin+Silodosin)

TRA: Trandolapril; ATE: Atenolol; CAR: Carteolol; NIC: Nicardipine; FEL: Felodipine; NIF: Nifedipine; NIS: Nisoldipine; DOX: Doxazosin; PAR Prazosin; WCC: world competitive contest algorithm; CUK: cuckoo; FOA: forest optimization algorithm; DSOS: discrete symbiotic optimization search.

Table 6. The outcomes of the proposed algorithm on the selected drugs

Given drug	Chemical formula	Proposed lists	Drugs of the list	Chemical formula	Similarity
Trandolapril	$C_{24}H_{34}N_2O_5$	(Cilazapril)	Cilazapril	$C_{22}H_{31}N_3O_5$	0.87
Atenolol	$C_{14}H_{22}N_2O_3$	(Esmolol)	Esmolol	$C_{16}H_{25}NO_4$	0.75
Carteolol	$C_{16}H_{24}N_2O_3$	(Xamoterol+Nebivolol)	Xamoterol	$C_{16}H_{25}N_3O_5$	0.80
			Nebivolol	$C_{22}H_{25}F_2NO_4$	0.58
Nicardipine	$C_{26}H_{29}NO_6$	(Cyclandelate+Nisoldipine),	Cyclandelate	$C_{17}H_{24}O_3$	0.49
		(Drotaverine+Nisoldipine)	Nisoldipine	$C_{20}H_{24}N_2O_6$	0.82
			Drotaverine	$C_{24}H_{31}NO_4$	0.71
Felodipine	$C_{18}HCl_2NO_4$	(Pinaverium+ Nisoldipine)	Pinaverium	$C_{26}H_{41}BrNO_4$	0.35
			Nisoldipine	$C_{20}H_{24}N_2O_6$	0.57
Nifedipine	$C_{17}H_{18}N_2O_6$	(Pinaverium + Nisoldipine)	Pinaverium	$C_{26}H_{41}BrNO_4$	0.35
			Nisoldipine	$C_{20}H_{24}N_2O_6$	0.90
Nisoldipine	$C_{20}H_{24}N_2O_6$	(Pinaverium+Isradipine),	Pinaverium	$C_{26}H_{41}BrNO_4$	0.40
		(Pinaverium+Drotaverine+Nilvadipine)	Isradipine	$C_{19}H_{21}N_3O_5$	0.83
			Drotaverine	$C_{24}H_{31}NO_4$	0.69
			Nilvadipine	$C_{19}H_{19}N_3O_6$	0.85
Doxazosin	$C_{23}H_{25}N_5O_5$	(Nicergoline)	Nicergoline	$C_{24}H_{26}BrN_3O_3$	0.50
Prazosin	$C_{19}H_{21}N_5O_4$	(Dapiprazole),	Dapiprazole	$C_{19}H_{27}N_5$	0.69
		(Nicergoline+Tamsulosin),	Nicergoline	$C_{24}H_{26}BrN_3O_3$	0.47
		(Nicergoline+Periciazine+Dapiprazole)	Tamsulosin	$C_{20}H_{28}N_2O_5S$	0.58
			Periciazine	$C_{21}H_{23}N_3OS$	0.53
			Dapiprazole	$C_{19}H_{27}N_5$	0.69

Figures

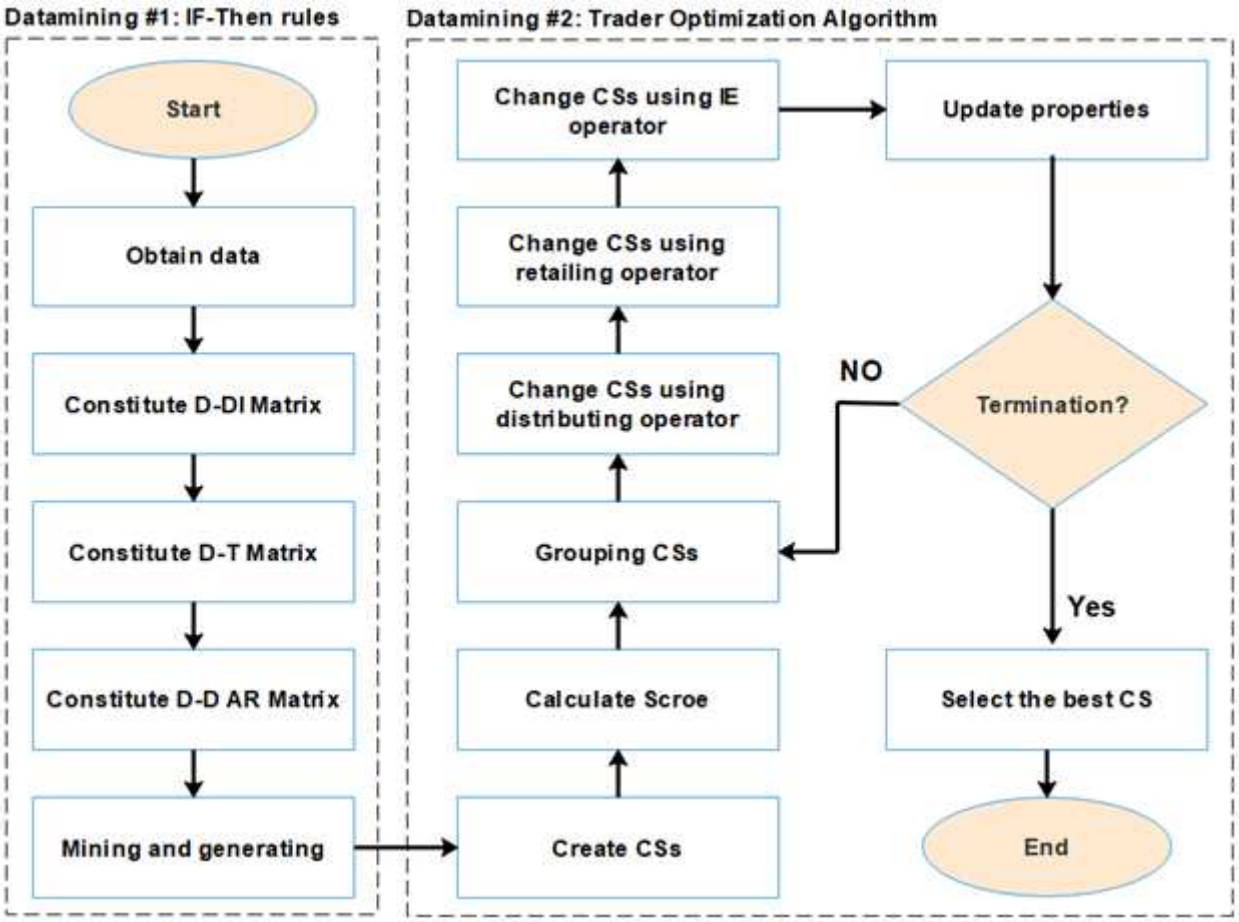


Figure 1

The framework of the proposed method. In the first step, the desired data are obtained from DrugR+ database. Next, drug-disease (D-DI), drug-target (D-T), and drug-drug-adverse reaction (D-D AR) matrices are constituted. Based on If-then rules, the drugs, which can affect targets related to HT, are acquired. In the second step, the proposed optimization algorithm (Trader) is applied to select a combination of drugs for the repurposing in HT.

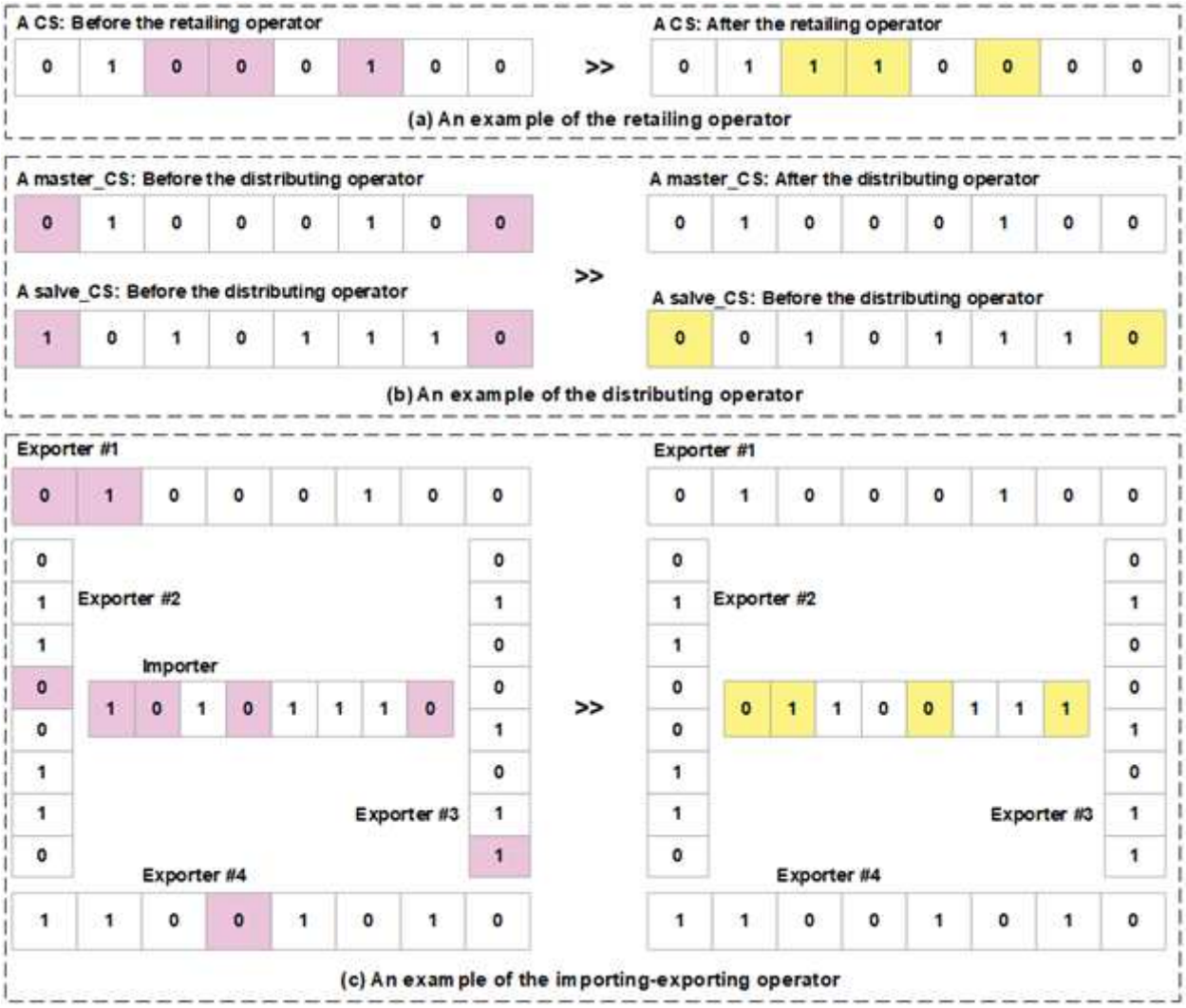


Figure 2

Trader's operators. (a) An example of the retailing operator: three points have been randomly chosen, and, then, their values have been updated by Eq. (9). This operator is only applied to slave_CSs. (b) An instance of the distributing operator: The master_CS selects two values from himself and distributes them into the slave_CS. (c) An example of the importing-exporting operator: The exporter CSs select some of their values and send them toward the importer CS. After applying the operators, the score function is called. Provided that the new score is better than the previous one, the changes are accepted. In contrast, the changes are ignored, the previous values are retrieved from the memory.

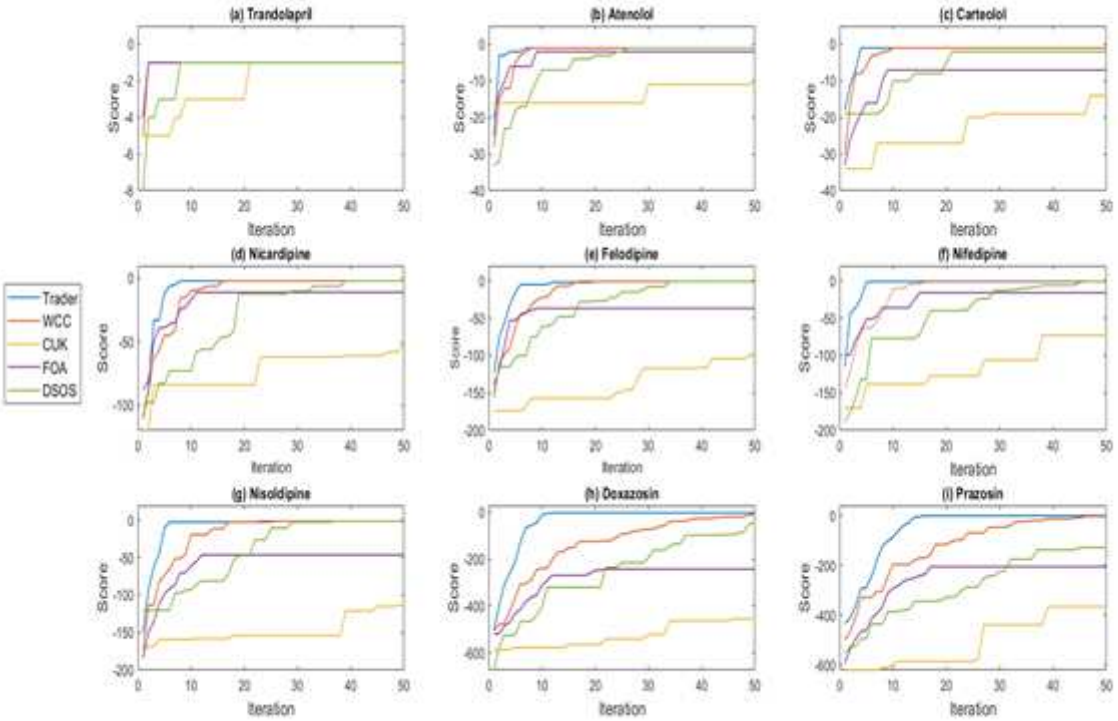


Figure 3

The convergence behavior of the algorithms on the generated datasets. (a) The convergence of the algorithms on the Trandolapril dataset. (b) The convergence of the algorithms on the Atenolol dataset. (c) The convergence of the algorithms on the Carteolol dataset. (d) The convergence of the algorithms on the Nicardipine dataset. (e) The convergence of the algorithms on the Felodipine dataset. (f) The convergence of the algorithms on the Nifedipine dataset. (g) The convergence of the algorithms on the Nisoldipine dataset. (h) The convergence of the algorithms on the Doxazosin dataset. (i) The convergence of the algorithms on the Prazosin dataset. For the datasets with the small sizes, the performance of the algorithms is almost the same. With enhancing the total number of candidate drugs (the size of the problem), the functionality of the algorithms differs from each other. From the proper convergence behavior, the algorithms can be considered as Trader, WCC, DSOS, FOA, and CUK, respectively.

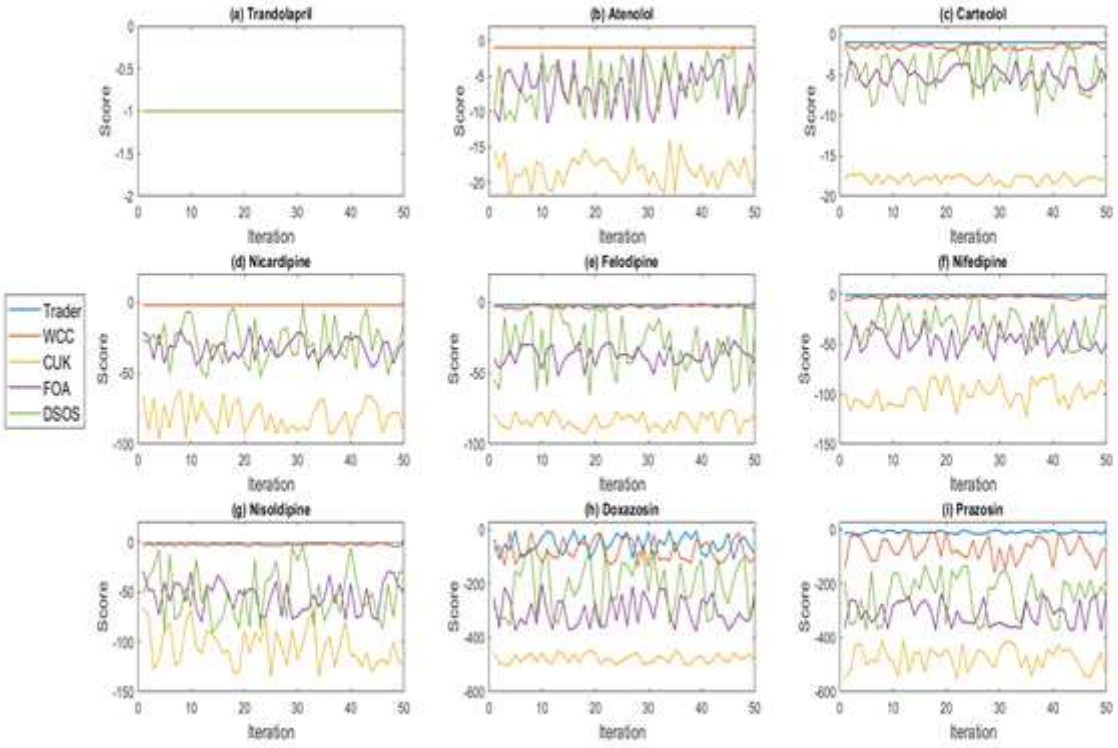


Figure 4

The stability behavior of the algorithms on the generated dataset. (a) The stability of the algorithms on the Trandolapril dataset. (b) The stability of the algorithms on the Atenolol dataset. (c) The stability of the algorithms on the Carteolol dataset. (d) The stability of the algorithms on the Nicardipine dataset. (e) The stability of the algorithms on the Felodipine dataset. (f) The stability of the algorithms on the Nifedipine dataset. (g) The stability of the algorithms on the Nisoldipine dataset. (h) The stability of the algorithms on the Doxazosin dataset. (i) The stability of the algorithms on the Prazosin dataset. Except for the Trandolapril and Nicardipine datasets, the Trader algorithm (proposed algorithm) is remarkably more stable than others and leads to better outcomes. Since the performance of other algorithms reduces with raising the total number of candidate drugs, the performance of the introduced algorithm (Trader) is better than others.