Human Protein Complex Signatures for Drug Repositioning

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ABSTRACT

Drug repositioning approaches are attracting more and more attentions in drug discovery field. Benefiting from the high-throughput gene expression data, many computational drug repositioning approaches use gene signatures to represent diseases and drugs, to identify potential drugs for diseases. Then the gene signature is used to identify potential drugs for a disease. However, the gene signatures do not take the dependencies between genes into account in the development of diseases. In this paper, we proposed human protein complex (HPC) signatures to identify potential drugs for diseases. The human protein complex (HPC) features are identified from the comprehensive resource of mammalian protein complexes (CORUM) database

Based on the gene expression values, the HPC expression values are calculated. All the gene expression profiles of diseases and drug perturbations are converted to the profiles of HPCs. The HPC signatures are identified from the profiles and a list of drug candidates is generated. The results of 5 cancers indicate that the proposed method identifies more known drugs, compared with gene signature methods.

CCS CONCEPTS

• **Applied computing → Bioinformatics**; *Bioinformatics*; *Bioinformatics*; Bioinformatics.

KEYWORDS

Drug Repositioning; Human Protein Complex; Gene Signature; LINCS; CMap

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1 INTRODUCTION

In the past decades, drug repositioning achieved a large progress in drug discovery. In traditional drug discovery approaches, a new drug often costs 8-10 years and 0.8-1.5 billion US dollars before it can be sold in the market [13]. To reduce such costs is the very first aim of drug repositioning. Drug repositioning has brought some drugs to the market, such as sildenafil for erectile dysfunction [5] and retinoic acid for acute promyelocytic leukemia [2].

The initial drug repositioning approaches are phenotypic drug screening and target-based methods [29]. Between 1999 and 2008, 28 small molecules were identified by phenotypic drug screening and 17 were proposed by target-based methods [26, 64]. However, the efficiency of both phenotypic drug screening and target-based methods are limited. As an improvement, the computational approaches are able to study almost all small compounds in short time and identify drug candidates in great efficiency [73].

Benefiting from the applications of high-throughput technologies and databases, many computational approaches are used in drug repositioning studies, including pathway-based methods [66, 89], similarity-based methods [82, 83], network-based methods [27, 43, 84, 90], signature-based methods [22, 51, 56], *et al.* The signature-based methods put more attentions on the genes whose expression values are significantly changed during disease development. Many gene expression databases are proposed to make those methods more efficient.

In 2006, Lamb *et al.* proposed a drug perturbation database named Connectivity Map (CMap), where a large number of gene expression profiles under specific drug perturbation cultures are encompassed [33, 34]. In their work, a gene signature is used to represent a biological condition and a rank-based matching strategy based on the Kolmogorov-Smirnov statistic [24] is used to calculate the connection score between a gene signature of a disease and a drug perturbation profile. The drug candidates are the drugs which have satisfied the connection scores. In 2008, Zhang *et al.* proposed a simpler and more robust matching method based on CMap database, named statistically significant connections' map (sscMap), where

the statistic significance of all connections were calculated [87, 88]. Wen *et al.* used the sscMap method to study drug candidates for colorectal cancer [77].

However, one significant limitation of CMap is the data coverage. Only 5 cell lines and approximately 1300 small molecules are encompassed. Among them, the number of Food and Drug Administration (FDA)-approved drugs are even smaller. In 2015, the Library of Integrated Network-Based Cellular Signatures (LINCS) program was proposed to create a network-based understanding of biology [63]. The drug perturbation database is an important component of the LINCS program. The LINCS database Phase I, which encompassed 1,319,138 profiles, approximately 70 cell lines and 20,000 small compound perturbations, was published in 2015. Based on the LINCS database, researchers use gene signature-based methods to study drug repositioning [51].

In both CMap and LINCS database, each drug perturbation expression profile is based on gene features. The disease profiles, which are used to identify a gene signature, are also series of genes expression values. The gene signatures are the connections between drug perturbation profiles and diseases. In those methods, genes are considered as independent elements to represent a disease or a drug. Actually genes work together in terms of protein complexes in the development of diseases [19, 38, 40, 55].

To reflect the dependencies of genes in signatures of a disease, we use protein complexes to represent a disease in drug repositioning. A protein complex is a group of proteins that work together in a certain biological process. Proteins in a complex are highly interactive with each other [7, 36]. In our method, we use the human protein complexes (HPCs) to reflect the interactions and co-operations among genes and products. Those HPC signatures are identified from the comprehensive resource of mammalian protein complexes (CORUM) database. Since each HPC compresses a number of genes, the gene expression profiles of diseases are replaced by disease-HPC expression profiles. Then a HPC signature is identified from the HPC profiles. Meanwhile, the drug perturbation profiles in LINCS are also converted into drug perturbation-HPC profiles. Finally, a connection method is used to calculate the connection scores between a HPC signature and drug perturbation-HPC profiles, and a list of drug candidates are generated.

To illustrate the performance of our proposed method, we compare it with two gene signature methods. All the three methods are examined in data sets of 5 cancers. In each experiment, the top 20 small compounds in the result are identified as a list of drug candidates. Among them, the drugs whose treatment has been studied are known drugs and other drugs in the list are potential drugs. The number of known drugs in a list is utilized as an evaluation matric. The HPCDR method identifies the largest number of known drugs among all three competing methods. Additionally, we study the annotations of the drugs in DrugBank database. Some known drugs and potential drugs have been identified as antineoplastic agents.

2 MATERIALS AND METHODS

To identify new potential treatments of old drugs, we propose a novel approach, named HPCDR, to study drug repositioning. The HPCDR method identifies human protein complex (HPC) signatures, instead of gene signatures. Figure 1 illustrates the flowchart of the HPCDR method. Figure 1.A, 1.B and 1.C discribe the databases used in HPCDR. Drug perturbation profiles are from the LINCS database Phase I. Human protein complexes are from the CORUM database. Microarray data are from GEO database and mapped to Entrez gene profiles. Figure 1.D and 1.E illustrate the next steps. Both drugs and diseases profiles are mapped to HPC profiles by taking the mean of values of all genes belonging to a HPC. Figure 1.F is the process to identify a HPC signature from the disease profiles. Then the connection scores between the HPC signatures and the drug perturbation-HPC profiles are calculated. All the scores are sorted in ascending order and the top N drugs are identified as drug candidates for that disease.

Table 1: The disease datasets

Disease	GEO serial numbers	Platforms	Number of samples
Breast Cancer	GSE10780	GPL570	84
	GSE15852	GPL96	86
	GSE50948	GPL570	80
Cervical Cancer	GSE63514	GPL570	48
Colorectal Cancer	GSE21510	GPL570	70
	GSE41258	GPL96	88
	GSE49355	GPL96	30
Kidney Cancer	GSE66272	GPL570	54
Lung Cancer	GSE10072	GPL96	48
	GSE19804	GPL570	96
	GSE27262	GPL570	50

2.1 Datasets

In this paper, the gene expression profiles are downloaded from the Gene Expression Omnibus (GEO) database [3], which is built by the National Center for Biotechnology Information (NCBI). It archives microarrays and other forms of high-throughput genomic data. In our study, we downloaded the microarray data of 5 cancers, which represent the expression values of a number of genes. In the GEO database, the number of data sets of a specific cancer is very large. However, many of the datasets contain only tumor tissue samples. To achieve a meaningful signature from a data set, we utilize the data set which contains both tumor and normal tissue samples. Each tumor tissue sample has a corresponding normal tissue sample. The details of the datasets are listed in Table 1.

Besides the gene expression profiles of diseases, we generate the drug perturbation profiles from the LINCS database. Many types of perturbations are compassed in the database, including 19,811 small compound drugs, 18,493 shRNAs, 3,462 cDNAs and 314 biologics. To ensure the small compound drugs are safe, we concentrate on the profiles of FDA-approved drugs in our study. The number of generated profiles is 152,290.

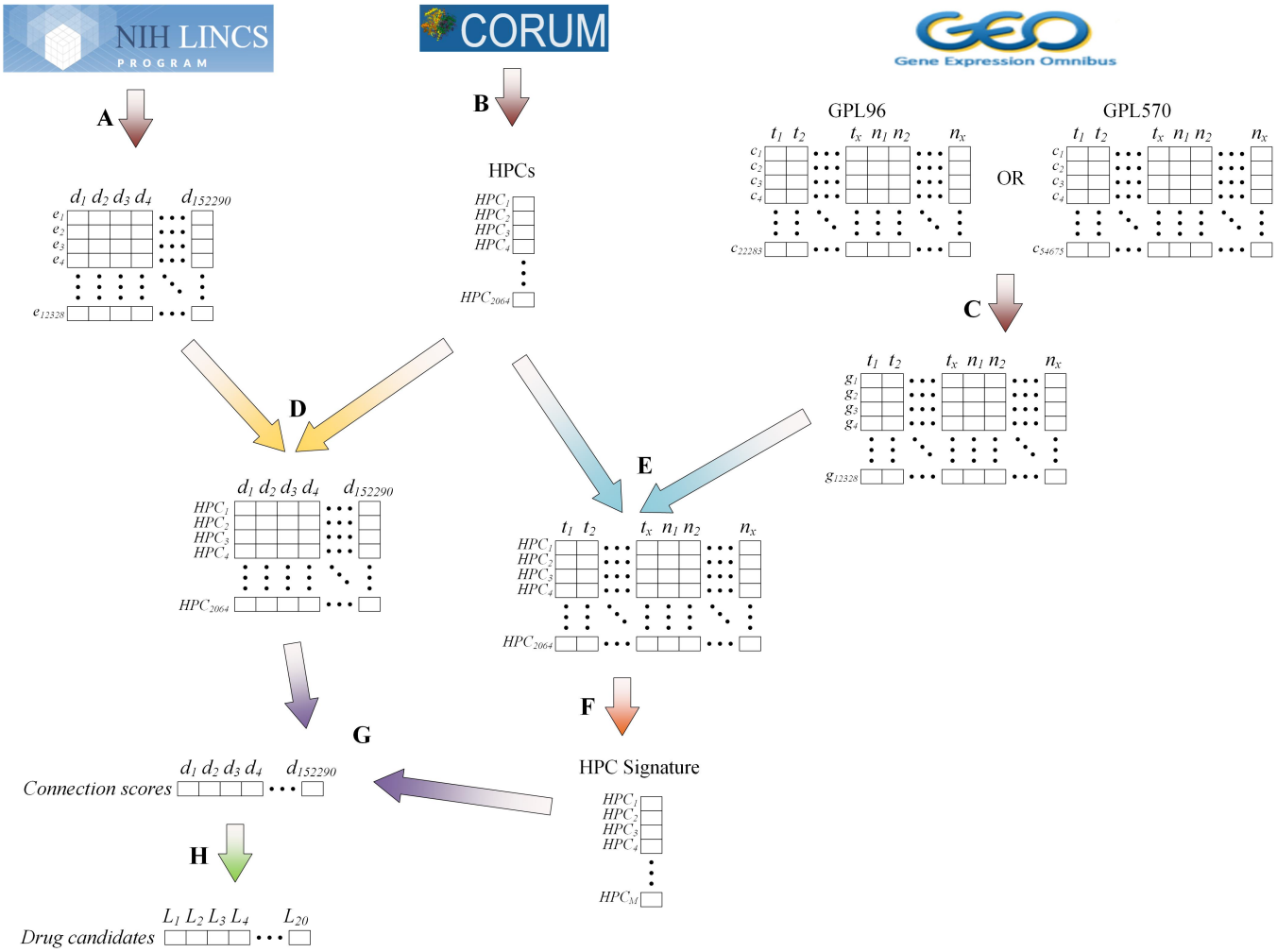

Figure 1: The flow chart of our HPCDR method.

(A): The drug perturbation profiles are from the LINCS database. (B): HPCs are selected from the CORUM database. The number of satisfied HPCs is 2,064. (C): Microarray data were downloaded from Gene Expression Omnibus (GEO) database. The microarray data is mapped to Entrez genes profile. (D): Based on the HPCs, drug perturbation profiles in LINCS database are converted into drug perturbation-HPC expression profiles. (E): Based on the HPCs, the Entrez gene expression profiles of a disease are converted into disease-HPC expression profiles. (F): An HPC signature is identified from the disease-HPC expression profiles. (G): A connection method is used to calculate 152,290 connection scores between the HPC signature and profiles. (H): The connection scores are sorted in ascending order and the top 20 perturbations are identified as drug candidates.

2.2 HPCs

In previous studies, the drug repositioning methods paid attention on gene signatures, that each gene is considered as an independent unit. However, genes often interacted with each others in complex diseases [80]. To reveal the dependencies of genes in cancers, many researchers studied proteins encoded by genes, and the roles of protein-protein interactions (PPIs) or protein complexes in cancers. Ivanov *et al.* illustrated that PPIs play an important role in tumor progression, invasion and/or metastasis [28]. Particularly, Li *et al.* proposed that the Hsp70-Bag3 PPI can be a potential target in cancer [40].

A protein complex is a group of proteins that are highly interactive with each other in a certain biological process [**?**]. The proteins in a complex play similar roles in a biological process. Sabatini illustrated the roles of mammalian target of rapamycin complexes (mTORCs) in pathways and tumors [55]. Fu *et al.* established essential roles of TWIST/Mi2/NuRD protein complex in cancer metastasis [19].

Furthermore, based on our study of PPIs and protein complexes, we consider human protein complexes (HPCs), instead of individual genes (proteins), to represent a disease in this study. All the HPC information are downloaded from the the comprehensive resource of mammalian protein complexes (CORUM) database. It compasses

4,275 protein complexes, among which there are 2,916 HPCs. Since a number of genes are contained in an HPC and the coding scheme in LINCS database is Entrez gene coding, the Entrez genes are used to connect HPC signature of a disease and LINCS drug perturbation HPC profiles. More importantly, all the genes in a HPC should be measured in LINCS database. The number of satisfied HPCs is 2,064. In the following section, all the profiles are converted into 2,064-dimensional vectors.

2.3 Data Pre-procession

In this study, the gene expression data from GEO database are obtained from GPL96 and GPL570 platforms, which compass 22,283 and 54,675 probe sets, respectively. All the data sets are normalized using robust multi-array average (RMA) method and log2-transformed. Because there are 22,277 common probe sets among the two platforms, we study the differences and similarities of the mapping of them and the other 32,398 probe sets. The 22,277 common probe sets are mapped to 12,315 Entrez genes and the other 32,398 probe sets are mapped to 12,321 Entrez genes. Only 6 Entrez genes are different. Then we choose the common probe sets to do the experiments. All gene expression profiles are converted to 22,277-dimensional vectors.

The second step is to map probe sets to Entrez genes. The drug perturbation profiles in LINCS database are obtained from L1000 platform, which contains 12,328 Entrez genes. Among them, there are 978 landmark genes and 11,350 inferred genes. The landmark gene expression values are measured directly from L1000 platform and the inferred gene expression values are calculated based on the landmark genes. Because an Entrez gene has a number of corresponding probe sets, the average gene expression value of those probe sets is used to be the expression value of the Entrez gene. Then both the profiles of diseases and drug perturbations are 12,328-dimensional vectors. Specifically, the expression values of landmark genes are on the top of the inferred genes, in order to make the experiments more convenient.

The third step is to select HPCs from Entrez genes. In CORUM database, most of HPCs contain less than 10 genes. The HPC expression value is the average expression value of genes that belong to it. Then all the Entrez gene expression profiles of diseases and drug perturbations are converted into 2,064-dimensional HPC expression profiles.

2.4 HPC Signatures

In this section, we identify the HPC signatures from the HPC expression profiles of diseases. An HPC can be represented by a 2x-dimensional vector $(t_1, \ldots, t_x, n_1, \ldots, n_x)$, where t_i is the expression value of the HPC in disease tissue profile T_i and n_i is that in normal tissue profile N_i. The fold change ratio r is calculated, based on the average value of *HPC* in disease tissues and normal tissues. Only the HPC whose fold change ratio is larger than 2 is considered as a member of the HPC signature.

Then the paired t-test is used to calculated the statistical significance of the HPCs. The disease-normal difference of HPC_i is denoted as $diff = (t_1 - n_1, t_2 - n_2, \ldots, t_x - n_x)$. Then the *T-score* is calculated as follows:

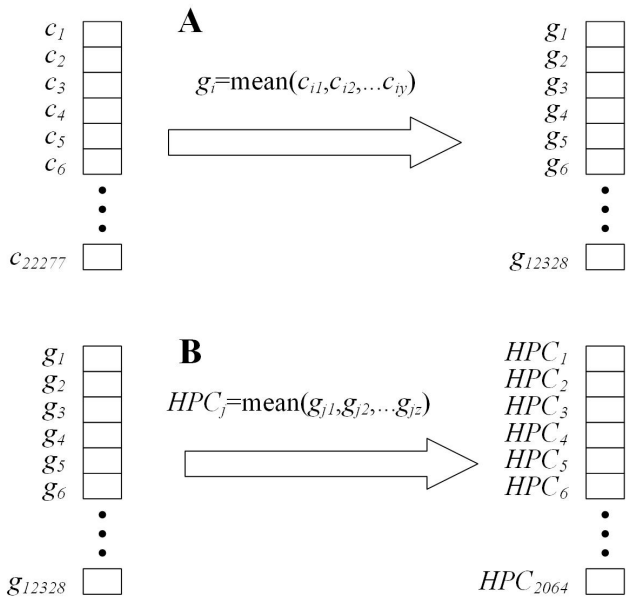

Figure 2: The details of the conversion.
A: From a gene expression profile of a disease to a profile of Entrez genes. B: From a profile of Entrez genes to that of HPCs.

$$T\text{-}score = \frac{\mu \times \sqrt{x}}{\sigma} \tag{1}$$

where μ is the average value of *diff* and σ is the standard deviation of *diff*.

Then a p-value is assigned from the *T-score*, and the HPCs are sorted in ascending ordert according to their p-values. The False Discovery Rate (FDR) α is set to be 0.01 and is controled by the Benjamini-Hochberg procedure [4] as follows:

$$p(M) \leq \frac{M}{H}\alpha \tag{2}$$

where H is the number of HPCs in the profile. An HPC whose p-value is smaller than the threshold is identified as a significant HPC. The largest HPC signature length M is 100 to assure that $p(M) \leq 1/H$ so that the maximum number of false HPCs in the signature is 1.

In our experiments, the t-test is calculated in each dataset independently. Each dataset has the same number of normal and tumor profiles to apply the paired t-test.

for disease with one dataset, the HPCs whose fold change ratio is larger than 2 and p-value is smaller than $1/H$ are identified and sorted in ascending order based on their p-values. The top M HPCs are identified as the HPC signature of the disease.

For diseases with more than one dataset, in each dataset, the HPCs are sorted in ascending order according to their p-values. Each HPC in a dataset has a rank score of $(H+1-R)/H$, that R is its rank in the dataset. If the fold change ratio of an HPC is less than 2, then its rank score is set to be 0. The rank scores of an HPC in all datasets of a disease are summed up and all features are sorted

in descending order according to their total rank scores. The top M HPCs are identified as the HPC signature of the disease.

2.5 Matching Method

In this section, we use a method to calculate the connection score between a HPC signature and drug perturbation-HPC expression profiles, which is proposed originally to calculate connection scores between a gene signature and CMap profiles [77].

Firstly, the drug perturbation-HPC profile $P = \{pv_1, pv_2, \ldots, pv_H\}$ is replaced by a rank list $PR = \{pr_1, pr_2, \ldots, pr_H\}$, where pv_i is the expression value of HPC_i and pr_i is its rank in the list. The HPC with the smallest expression value is given a rank of H and the largest one has a rank of 1.

Meanwhile, the HPC signature is divided into two lists, one contains all up-regulated HPCs and another contains all down-regulated HPCs. The up-regulated HPC list indicates that it has a larger expression value in disease tissues than that in normal tissues, while a down-regulated HPC list indicates that it has a smaller expression value in disease tissues than that in normal tissues. Then the *up-score* and *down-score* is calculated as follows:

$$up\text{-}score = \sum_{i=1}^{H_{up}} (H + 1 - pr(i)) \tag{3}$$

$$down\text{-}score = -\sum_{j=1}^{H_{down}} (H + 1 - pr(j)) \tag{4}$$

where H_{up} is the number of HPCs in the up-regulated list and H_{down} is the number of HPCs in the down-regulated list. H is the same variable as mentioned in Section 2.4. *pr(i)* is the rank of HPC i in the drug perturbation-HPC list *PR*.

Then a possible maximum connection score is calculated as follows:

$$poss = \sum_{i=1}^{M} (H + 1 - i) \tag{5}$$

Then a connection score between a HPC signature and a drug perturbation-HPC profile is calculated as follows:

$$H\text{-}score = \frac{up\text{-}score + down\text{-}score}{poss} \tag{6}$$

In general, its range is [-1,1], a negative score indicated that the drug perturbation has a negative effect on the HPC signature, which means that the drug has a potential treatment on the disease.

All drug perturbations are sorted in ascending order according to their connection scores and the top N drugs are considered as drug candidates for the disease. Since a drug perturbation has more than one profile in the LINCS database, we may have some replicates of a drug among the top N drugs.

3 EXPERIMENTS AND RESULTS

3.1 Parameters and Performance evaluation

To evaluate the performance of drug repositioning methods, the most commonly used metric is the number of known drugs which are identified by the methods. The known drugs are the drugs whose treatments of a disease have been studied and indicated. In the experiments, given a HPC signature of a disease, we sort the connection scores of all drug perturbation-HPC profiles in descending order and identify the top 20 small compound drugs as the drug candidates for the disease. We compare our proposed HPCDR with two state-of-the-art methods.

To analyze the treatments of drugs, we study the annotations in DrugBank database [79]. Some drugs have been identified as antineoplastic agents in DrugBank, that their anti-tumor treatments have been studied. Additionally, the propagation of cancer is a process involving the participation of a number of enzymes that help develop new drugs [61]. In this study, we also consider the drugs which have been identified as enzyme inhibitors.

3.2 Compared With Other Methods

3.2.1 Entrez Gene Signatures. In this study, we replaced the gene signature with the HPC signature of a disease for drug repositioning. To illustrate the performance of our proposed method, we used Entrez genes to identify signatures directly and made a comparison with our method.

In this section, all the gene expression profiles of diseases are converted into profiles of Entrez genes, which are 12,328-dimensional vectors. Similar with our HPCDR method, we use T-test statistical method to identify DEGs from gene expression profiles of disease and normal tissue samples. Then we calculate the connection scores with drug-perturbation profiles and sort the scores in ascending order. To make a comparison, the top 20 small compound drugs are identified as drug candidates.

3.2.2 Landmark Gene Signatures. Our proposed method used HPC signatures instead of Entrez gene signatures, which can be seen as a feature extraction method. We also compared it with a feature selection method, that we identify landmark gene signatures from Entrez genes. The LINCS drug perturbation profiles contain 12,328 Entrez genes, among those there are 978 landmark genes and 11,350 inferred genes. The expression values of landmark genes are measured directly from the L1000 platform, which can represent approximately 82% information [63]. The expression values of inferred genes are calculated based on the landmark genes.

In this section, the gene expression profiles of diseases are represented by the profiles of landmark genes. The connection scores between disease profiles and drug-perturbation profiles are calculated. The top 20 drug perturbations are identified as drug candidates.

3.2.3 Comparison. In this section, our proposed method is compared with two competing methods described in the previous two subsections. Because the three methods are focused on three types of signatures, the results may be a little different. To make a better comparison, we generate the number of known drugs among top N on the result lists. As the number of connection scores of a disease signature is 152,290, to reduce the scale of drug candidates and focus on the most possible drugs, we set the variable N to be 20. The number of known drugs are listed in Table 2. Since one drug has a number of profiles in LINCS database. They have different concentrations, durations or cell lines. One drug may appear several times among the top 20 drug candidates. Based on the results of known drugs, other drugs, which are false positive in the experiments, are lacking of clinical trials. However, that doesn't mean

Table 2: The number of known drugs identified by our HPCDR method and two gene signature method

Disease	HPCDR	Entrez gene signatures	Landmark gene signatures
Breast Cancer	12	9	10
Cervical Cancer	10	6	2
Colorectal Cancer	13	8	6
Kidney Cancer	5	2	1
Lung Cancer	10	5	6

they are ineffective drugs. They are potential drugs that may have treatment for the given disease.

The results indicates that our proposed method can identify the most number of known drugs from the five disease data sets. Among 4 out of 5 cancers, the HPCDR method can generate at least 10 known drugs. In kidney cancer, the HPCDR method only identifies 5 known drugs. For the method of Entrez gene signature, the largest number of known drugs is 9. Especially in kidney cancer, only 2 known drugs are obtained. The third method is about landmark gene signature, it only identifies 2 known drugs in cervical cancer and 1 known drugs in kidney cancer. In other three cancers, it generates similar number of known drugs with Entrez gene signatures.

3.3 Analysis of Predictions

In this section, we utilize some literature evidences and annotations in the Drugbank database to analyze the treatments of the drugs which are identified by our method.

3.3.1 Breast Cancer. In the results, 5 of the identified drugs are antineoplastic agents, including aminoglutethimide, dexamethasone, resveratrol, vinorelbine and vorinostat. Aminoglutethimide has been recognized as a valuable treatment for breast cancer since 1980s [45]. Dexamethasone is a type of corticosteroid medication, which enhances the effects of ADR on induction of apoptosis and inhibition of cell proliferation [74]. It can also enhance drug efficiency [25]. Resveratrol is type of natural phenol, which decreases angiogenesis and increases cell apoptosis in vitro and mice experiments [20]. Vinorelbine is an anti-mitotic chemotherapy drug that has beed used in the treatment of breast cancer. Vorinostat is a member of histone deacetylases(HDAC) inhibitors. The combination of vorinostat and tamoxifen decrease resistance in breast cancer patients [48].

Besides antineoplastic agents, 5 other drugs are identified as enzyme inhibitor, including atorvastatin, disulfiram. itraconazole, LY-294002 and ouabain. Atorvastatin is a statin medication, that statins increase cell apoptosis, inhibit proliferation and drease metastatic dissemination of breast tumors [71]. The disulfiram-copper complex has the potential to inhibit the proteasomal activity in breast cancer cells [8]. Itraconazole is a member of triazole medication family, which inhibits brease cancer cell proliferation [75]. LY-294002 is a phosphoinositide 3-kinase (PI3K) inhibitor. It down-regulates antiapoptotic proteins and sensitize cerulenin-induced apoptosis in breast cancer cells [57]. Ouabain is a cardiac glycoside, and can be used medically in lower doses. The combination of digoxin, proscillaridin A and ouabain induces apoptosis in breast cancer cells [78]. Besides, nitazoxanide induces breast cancer cell apoptosis and suppresses tumor growth [17].

Table 3: The drugs identified by our HPCDR method

Disease	Known drugs	Potential drugs
Breast Cancer	aminoglutethimide, atorvastatin, dexamethasone, disulfiram, itraconazole, LY-294002, nitazoxanide, ouabain, resveratrol, vinorelbine, vorinostat	tetracycline, milrinone, nizatidine, clemastine, molsidomine, nimodipine, tolazamide, cefazolin
Cervical Cancer	etoposide, genistein, LY-294002, niclosamide, sirolimus, thioridazine, wortmannin	idarubicin, mitoxantrone, danazol, afatinib, capsaicin, doxepin, tretinoin, digoxin, ABT-751
Colorectal Cancer	atorvastatin, BMS-777607, gefitinib, mitoxantrone, olaparib, saracatinib, vorinostat, zebularine	BMS-777607, mitoxantrone, aliskiren, eplerenone, nifedipine, nimodipine, terconazole
Kidney Cancer	cediranib, panobinostat, tivozanib, vorinostat	brivanib, trimethobenzamide, clofibrate, lorazepam, rivaroxaban, ozagrel, nizatidine, mosapride, ritodrine, exemestane, iniparib, treprostinil, temozolomide, thenoyltrifluoroacetone
Lung Cancer	calcitriol, chlorambucil, entinostat, foretinib, ibuprofen, iloprost, MK-1775, olaparib, pravastatin, tacedinaline, troglitazone, warfarin	fursultiamine, etomidate, fluvoxamine, methantheline, mosapride, trazodone, prazosin

Among the potential drugs whose treatments for breast cancer have not been proposed, there are also two drugs tetracycline and milrinone, identified as enzyme inhibitors. Particularly, tetracycline analogues have shown treatments for prostate cancer [44] and colorectal cancer [50].

3.3.2 Cervical Cancer. In the identified drug list, 6 out of 7 drugs are either antineoplastic agents or enzyme inhibitors. Etoposide is a member of topoisomerase inhibitor family. The combination of etoposide and cisplatin is safe and effective for cervical cancer [76]. Genistein is an angiogenesis inhibitor. It inhibits cell growth in cervical cancer cells [32]. LY-294002 and wortmannin are two PI3K

inhibitors, that enhance ratio sentivity and increase apoptosis [35]. The combination of niclosamide and paclitaxel has been used in the treatment of cervical cancer, where niclosamide sensitizes the responsiveness of cervical cancer cells to paclitaxel [10]. Sirolimus, also known as rapamycin, has a similarity treatment of enhancing the sensitivity of cervival cancer cells to paclitaxel [18]. The last drug thioridazineis neither antineoplastic agent nor enzyme inhibitor, it induces apoptosis in cervical cancer cells [31].

Among the potential drugs, idarubicin, mitoxantrone, afatinib, tretinoin and digoxin are either antineoplastic agents or enzyme inhibitors. Particularly, the studies of mitoxantrone [47] and digoxin [42] for prostate cancer, afatinib [81] and tretinoin [58] for lung cancer, have been proposed. The potential treatments of those drugs for cervical cancer should be studied in the future.

3.3.3 Colorectal Cancer. In the results of colorectal cancer, atorvastatin and vorinostat have shown treatments for breast cancer in previous section. Atorvastatin is effective in inhibiting colorectal cancer cells, in combination with celecoxib and aspirin [54]. The combination of vorinostat and bortezomib shows synergistic antiproliferative and proapoptotic effects in colorectal cancer cells [52]. BMS-777607 is a MET tyrosine kinase inhibitor, that has shown promising results in colorectal cancer [16]. Gefitinib is a drug used in the treatment of certain types of cancer [70]. Mitoxantrone is anthracenedione antineoplastic agent, it shows moderately effective in advanced colorectal cancer cells [12]. Olaparib is a type of poly-ADP ribose polymerase (PARP) inhibitors, which makes colorectal cancer cells sensitive to it [72]. Saracatinib is a a dual kinase inhibitor, which has been investigated for the treatments of cancers. It decreases tumor growth in colorectal cancer cells [1]. Zebularine shows anti-tumor activity in colorectal cancer cells [85].

There are 7 potential drugs that their treatments for colorectal cancer can be studied in the future. Particularly, the treatments of BMS-777607 [59] and mitoxantrone for other cancers has been proposed.

3.3.4 Kidney Cancer. All of the four identified drugs are both antineoplastic agents and enzyme inhibitors. Cediranib demonstrated significant anti-tumor activity in the treatment of kidney cancer, that its efficacy parameters is comparable to approved drugs [62]. Panobinostat is a non-selective HDAC inhibitor, which inhibits kidney cancer cells [49]. Tivozanib is a vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor and has been recommended in the treatment of advanced kidney caner [15]. Vorinostat also shows treatment for kidney cancer [23].

15 potential drugs are identified in the results. Among them, the studies of brivanib [60], exemestane [21], iniparib [41] and clofibrate [6] for other cancers have been proposed.

3.3.5 Lung Cancer. In the results, 5 out of 12 identified knonw drugs are erther antineoplastic agents or enzyme inhibitors, including chlorambucil, entinostat, ibuprofen, olaparib and pravastatin. Chlorambucil has been used as antineoplastic agent for the treatment of various malignant and nonmalignant diseases [11]. The combination of chlortetracycline, nitrogen mustard and prednisone in lung cancer has been studied [30]. Entinostat is an HDAC inhibitor, which has shown promise in treating lung cancer [68]. Ibuprofen is a medication in the nonsteroidal anti-inflammatory drug, which can enhance the antitumoural activity of cisplatin in lung cancer [14]. Additionally, many drugs show treatment in lung cancer when combined with cisplatin. Calcitriol has shown antiproliferative effects either as a single agent or combined with cisplatin [53]. Olaparib is a PARP inhibitor, the combination of cisplatin with olaparib is more effective than each agent individually [46]. Pravastatin is a statin medication, which reduces progression and limits metastatic diffusion of established hepatocellular carcinoma [67].

Among other known drugs, MK-1775 and tacedinaline have been used in trials studying the treatment of Lung Cancer [9, 65]. Foretinib [37], iloprost [69], troglitazone [39] and warfarin [86] also have treatments in lung cancer.

4 CONCLUSIONS

Identification of signatures is an import component in computational drug repositioning approaches. In this study, we have proposed a signature identification method, named HPCDR, for drug repositioning. HPCDR generates HPCs from CORUM database. Both the gene expression profiles of diseases and the drug perturbation profiles are converted into the form of HPC profiles. The experiments of 5 cancers indicate that our HPCDR method identifies more known drugs than other two gene signature methods. The annotations from DrugBank are used to describe the treatments for cancers. In future studies, we would study more applications of HPC signatures in drug repositioning and device other kind of signatures.

5 ACKNOWLEDGMENTS

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