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A bidirectional drug repositioning approach for Parkinson's disease through network-based inference

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ABSTRACT

Parkinson's Disease (PD) is one of the most prevailing neurodegenerative disorders. Novel computational approaches are required to find new ways of using the existing drugs or drug repositioning, as currently there exists no cure for PD. We proposed a new bidirectional drug repositioning method that consists of Top-down and Bottom-up approaches and finally gives information about significant repositioning drug candidates. This method takes into account of the topological significance of drugs in the tripartite Indication-drug-target network (IDTN) as well the significance of their targets in the PD-specific protein–protein interaction network (PPIN). 9 non-Parkinsonian drugs have been proposed as the significant repositioning candidates for PD. In order to find out the efficiency of the repositioning candidates we introduced a parameter called the On-target ratio (OTR). The average OTR value of final repositioning candidates has been found to be higher than that of known PD specific drugs.

1. Introduction

Parkinson's disease (PD) is one of the most prevailing neurodegenerative disorders. It is the second most common degenerative disorder after Alzheimer's disease, affecting more than 1% of those over the age of 55 years and more than 3% of those over the age of 75 years [1]. PD is characterized by tremor, muscle rigidity, and slowed movement (bradykinesia). The motor symptoms of PD result from the death of dopamine generating cells in the substantia nigra, a region of the mid brain. Development of new drugs is essential, as currently there exists no cure for PD.

Conventional method of drug design is a prolonged process and most of the drugs fail during the development [2]. Growing evidences suggest that drug repositioning, i.e. finding new indications for approved drugs, could be one of the most cost- and time-effective strategies to cope up with this problem [3]. An advantage of drug repositioning is that since the drug has already passed a significant number of validation tests, the risk of failure due to toxicity is reduced [4]. Currently many works exist on systematic drug repositioning [5–7]. In general, methods for systematic drug repositioning are either based on similarity of diseases or based on similarity of drugs [8]. Chiang & Butte [5] devised a method to reposition drugs based on the similar therapies shared by two diseases. Yang & Agarwal [6] proposed a method based on the common occurrence of clinical side effects. Supervised inference methods such as network-based inference have also been used to construct drug-target network (DTN) in order to predict drug-target interactions and infer repositioning candidates [7]. However a combination of similarity-based and network-based approach is rarely examined. Concepts of network science need to be efficiently combined with traditional similarity-based repositioning techniques in order to find the best possible repositioning candidates for a disease. Recently, Fukuoka et al. [8] devised a two-step drug repositioning method based on protein–protein interaction networks (PPIN) of genes shared by a pair of diseases and the similarity of drugs shared by the diseases. However, they did not take into account of the topological significance of target proteins in the PPIN that is an important virtue with respect to drug-target interaction prediction. A drug targeting a topologically significant

Abbreviations: PD, Parkinson's disease; IDTN, indication-drug-target network; PPIN, protein–protein interaction network; G_{geno}, set of genes provided by Genotator; G_{poly}, set of genes provided by PolySearch; G_{pes}, set of genes provided by Pescador; G_{final}, final set of PD-related marker genes; D_{final}, final set of drugs considered in our study; GCC, giant connected component; OTR, on-target ratio; TPD, number of PD-specific targets of a drug; T_{real}, actual number of targets of a drug.

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node in PPIN can be considered a promising candidate for repositioning.

In this context, we propose a bidirectional drug repositioning method which takes into account of the significance of drugs in the tripartite Indication-drug-target network (IDTN), as well as the significance of the drug targets in the PD-specific PPIN. This method contains Top-down and Bottom-up approaches. First, we constructed an IDTN consisting of PD-related marker genes, non-Parkinsonian drugs and pharmacological indications associated with them. Subsequently we constructed a PPIN consisting of PD-related marker genes. In the Top-down approach, we analysed the IDTN to find out highly connected drugs and then analysed the PPIN to find out the significance of proteins which are targeted by these drugs. In the Bottom-up approach, we started with the analysis of the PPIN to find out the topologically significant proteins and subsequently analysed the IDTN to find out the highly connected drugs associated with these target proteins. Combining both the approaches, it was observed that 9 non-Parkinsonian drugs viz., Diethylstilbestrol, Erlotinib, Lidocaine, Dasatinib, Nifedipine, Testosterone, Sorafenib, Nicardipine and Melatonin showed high connections in the IDTN as well as their target proteins showed high topological significance in the PPIN. Moreover these 9 drugs have higher average OTR (On-target ratio) value than the average OTR value of PD related drugs (0.61 vs 0.36). Thus these 9 drugs were proposed in our study as the most significant repositioning candidates for PD.

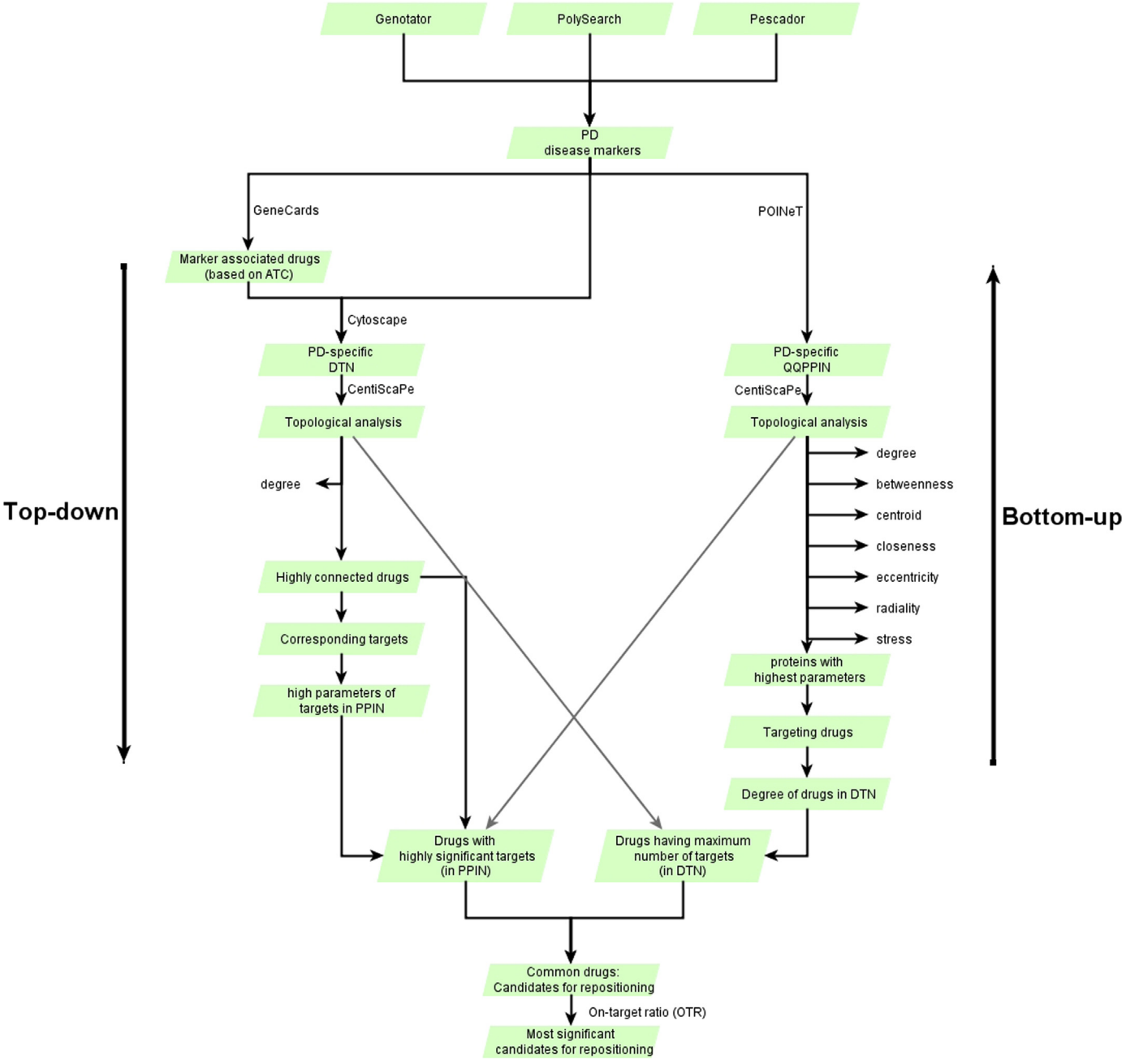


Fig. 1. Work flow of our study.

2. Materials & methods

The list of disease marker genes associated with PD was collected from three sources: a meta-database called Genotator [9] and two text mining systems - PolySearch [10] & Pescador [11]. The retrieved data was then manually annotated to convert names and aliases of the disease marker genes into their respective HUGO gene nomenclature committee (HGNC) symbols [12]. The final set of PD related marker genes (G_{final}) was derived from the union of genes obtained from Genotator, PolySearch and Pescador. The GeneCards database [13] was used to find out drugs associated with the genes and their corresponding proteins in G_{final}. The terms "gene" and "protein" are used interchangeably in our study. The PPIN for G_{final} was constructed using POINeT [14]. Detailed information regarding the drugs and their most significant pharmacological indications was collected from the DrugBank database [15]. Drugs labelled as "approved" in DrugBank and categorized in the Anatomical Therapeutic Chemical (ATC) Classification were only considered in this study. Drugs which are labelled "experimental" or "withdrawn" were not considered. The dataset was further screened to eliminate those drugs (D_{PD}) which were already known to be associated with PD. The set of remaining drugs (D_{final}) was considered as the final set and used in our repositioning study. Based on the binary interaction of the drugs in D_{final} with their target proteins in G_{final} and their pharmacological indications, the IDTN was constructed using the open source network analysis software Cytoscape [16]. Giant Connected Components (GCC) of both the networks (IDTN & PPIN) were formatted and visualized using the graph editing software yEd [17]. A Cytoscape plug-in called CentiScaPe [18] was used to perform the topological analyses of the IDTN and the PPIN. Degree or connectivity of nodes in the IDTN was analysed. Seven topological parameters viz., degree, betweenness, centroid, closeness, eccentricity, radiality and stress were considered to find out the significant nodes in the PPIN [19]. These significant nodes were used to perform the bidirectional drug repositioning study. On-target ratio (OTR) of PD-associated drugs and the drugs considered for repositioning was calculated as the ratio of the number of PD-specific targets (i.e., in G_{final}) of a drug (T_{PD}) to the total number of interactions of that drug (T_{real}) in DrugBank. Fig. 1 shows the work flow of our study.

3. Results & discussions

3.1. Collection of data and construction of the networks

A list of 2120 PD-related disease marker genes (G_{final}) were obtained from Genotator, PolySearch and Pescador were used to make independent queries in PubMed (www.ncbi.nih.gov/pubmed) to find out genes and corresponding proteins associated with PD. 966 drugs were found to be associated with these 2120 PD-related genes in G_{final}. Of these 966 drugs, 32 drugs were already known to be associated with PD. We eliminated these 32 drugs from our dataset and the remaining 934 drugs and their corresponding proteins were considered to constitute the PD-specific DTN. These 934 drugs and their corresponding target proteins constitute the PD-specific DTN. Then we searched the DrugBank to find out the pharmacological indications associated with each drug present in the DTN and constructed the PD-specific tripartite IDTN (Fig. 2A, B).

We used the POINeT web interface to construct the PD-specific PPIN (Fig. 3A) using the 2120 PD-related genes. POINeT takes any list of genes as input and gives a PPIN as an output. Since our input

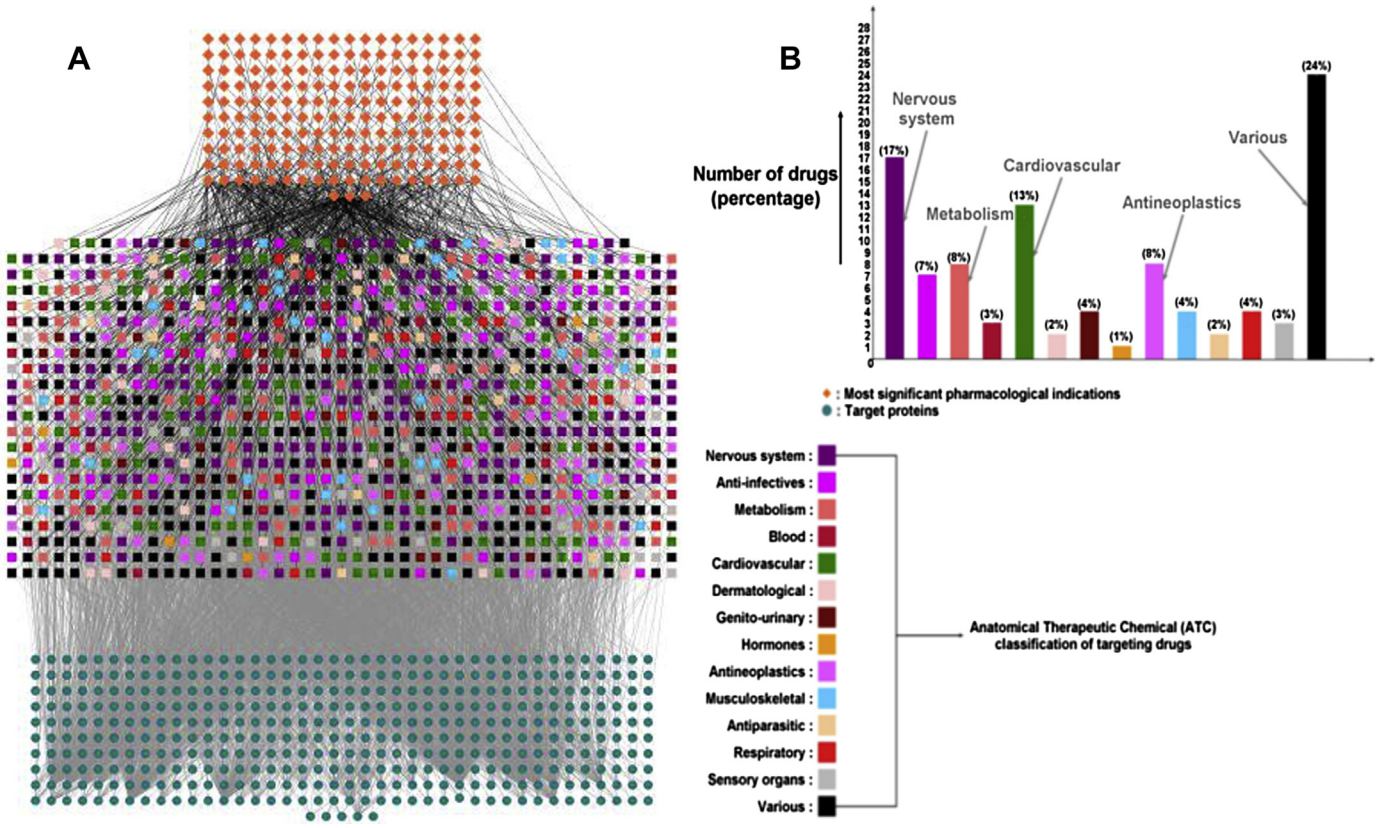


Fig. 2. A) Indication-drug-target network (IDTN) constructed in our study. Here the drugs are coloured according to the Anatomical Therapeutic Chemical (ATC) classification. B) Percentage distribution of the obtained drugs. Metabolism, Cardiovascular, Antineoplastics and various are the most dominant groups other than nervous system.

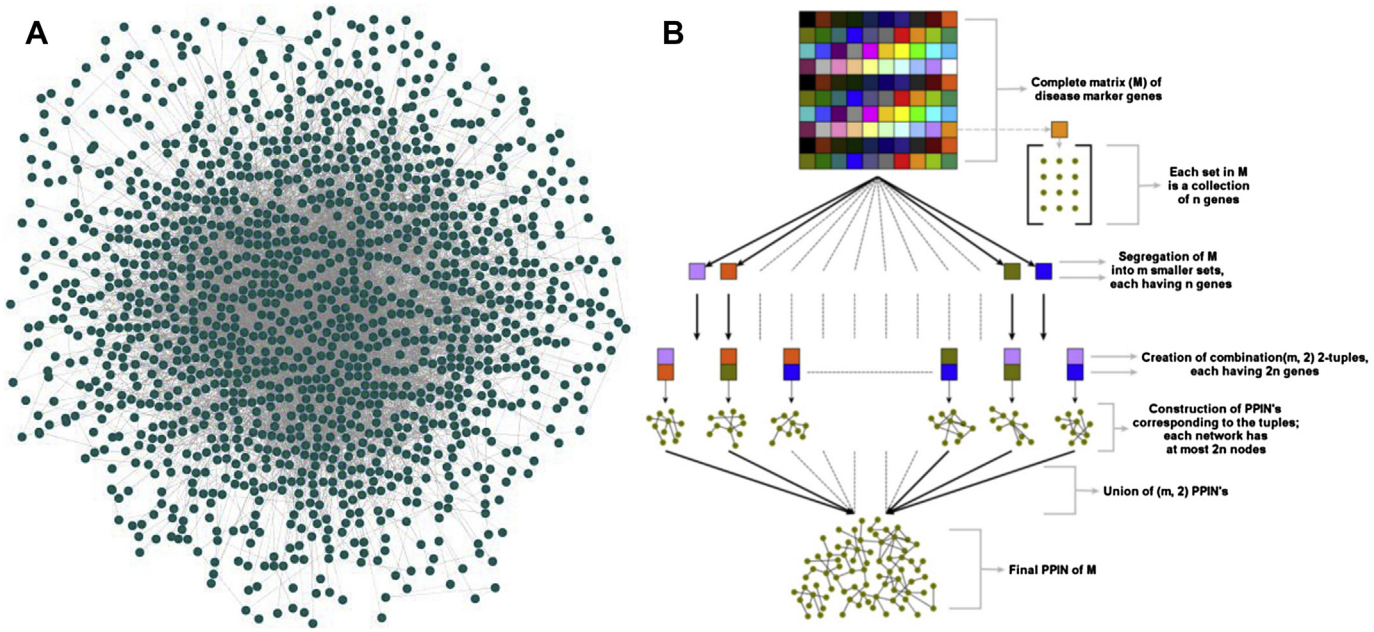


Fig. 3. A) Protein–protein interaction network (PPIN) constructed in our study. B) The method followed in order to construct the PPIN. In this figure, (m, 2) implies ${}^{m}C_{2}$.

PD-specific gene list consisted of more than 500 genes, we followed a new approach to construct the PPIN. We took the whole set (G_{final}) as a matrix (M) of m sets, where each set had n number of input genes. Then we created ${}^{m}C_{2}$ numbers of 2-tuples, each having 2n numbers of genes. Our target was to make 2n less than 500 (POINeT delivers good results if the list of input genes is smaller than 500). Correspondingly, we created PPINs for each of the ${}^{m}C_{2}$ tuples in POINeT and took the union of all the PPINs to get the final PPIN corresponding to G_{final} (Fig. 3B). In our case, we took m = 10 and n = 212 (i.e., 2n = 424 ≤ 500).

3.2. Statistical analysis of the networks

The IDTN contained a GCC having 1511 nodes: 923 drugs, 405 targets and 183 indications. CentiScaPe was used to analyse the degree distribution of nodes in the GCC of the IDTN (Supplementary file S1). The PPIN contained a GCC of 1378 nodes & 5445 edges. CentiScaPe was used to analyse seven different topological parameters viz., degree, betweenness, centroid, closeness, eccentricity, radiality and stress of nodes in the GCC of the PPIN (Supplementary file S2). Table 1 gives a brief description of the seven topological parameters used in this study along with their formulae [18,19].

3.3. Bidirectional drug repositioning

Following topological analyses of the PPIN and the IDTN we applied a bidirectional method to find out significant drugs for repositioning. This is a new method which takes into account two approaches (Top-down and Bottom-up) and finally gives information about significant repositioning drug candidates. Both the approaches and their corresponding results are discussed in the subsequent sections (Sections 3.3.1 and 3.3.2).

3.3.1. Top-down approach

In the Top-down approach, first we selected the hubs based on the degree of IDTN. In the IDTN, the highest degree of a drug was 28. 17 out of the 923 drugs in the IDTN showed degree greater than or equal to 50% of 28, i.e., 14. Therefore, in the Top-down approach, first we selected these 17 drugs (with degree ≥ 14) as hubs in the

Table 1
Network parameters used in our study & their biological significance: [18,19].

Parameter	Formula[a]	Biological significance in a PPIN
Degree	$\lvert\{u : u \subseteq V, (u,v) \in E\}\rvert$	Proteins with very high degree are interacting with several other proteins which suggests a central regulatory role.
Betweenness	$\sum_{s \neq v \neq t} \frac{\sigma_{st}(v)}{\sigma_{st}}$	High betweenness indicates relevance of a protein as functionally capable of holding together communication proteins.
Centroid	$\min\{\nu_v(u) - \nu_u(v) : u \in V\{v\}\}$	Proteins with high centroid values are possibly involved in coordinating the activity of other highly connected proteins, altogether devoted to regulation of a specific cell activity.
Closeness	$\frac{1}{\sum_{u \in V} dist(u,v)}$	A protein with high closeness is central to the regulation of other proteins but with some proteins not influenced by its activity.
Eccentricity	$\frac{1}{\max\{dist(u,v) : u \in V\}}$	Eccentricity can be interpreted as the easiness of a protein to be functionally reached by all other proteins in the network.
Radiality	$\frac{\sum_{u \in V}(\Delta G + 1 - dist(u,v))}{n-1}$	A protein with high radiality is central to the regulation of other proteins but with some proteins not influenced by its activity.
Stress	$\sum_{s \neq v \in V} \sum_{t \neq v \in V} \sigma_{st}(v)$	Stress of a protein indicates the relevance of a protein as functionally capable of holding together regulatory molecules.

[a] Symbols: $V \equiv$ set of nodes; $E = \{(u,v) : u, v \in V\} \equiv$ set of edges; $n = |V| \equiv$ number of nodes in V; $N\{v\} \equiv$ set of nodes connected to v; $\nu_u(v) \equiv$ number of vertex closer to u that v; $\Delta G \equiv$ diameter of the network; $dist(u,v) \equiv$ shortest path between u & v; $\sigma_{st} \equiv$ number of shortest paths between s & t wheres, $t \in E$; $\sigma_{st}(v) \equiv$ number of shortest paths between s& t passing through v.

IDTN and studied their specific targets. 122 targets were found for these 17 drugs in the IDTN. 105 out of these 122 targets were found to be participating in the PD-specific PPIN. Subsequently we analysed the topological significance of these 105 drug-target proteins in the PPIN. We sorted these 105 targets according to the 7 significant topological parameters considered in our study. We observed that among the 105 target nodes, top 3 nodes (AR, ALB and RAF1) showed significant degree, betweenness and stress values, top 2 nodes (AR, RAF1) showed significant radiality, closeness and centroid values and top 9 nodes (AR, RAF1, PDGFRB, NTRK1, FGFR1, ANXA1, FLT1, ALOX5, SHBG) showed significant eccentricity values (Fig. 4A). 9 Drugs corresponding to these targets were selected as the primary repositioning candidates viz., Halothane, Propofol, Testosterone, Olanzapine, Amitriptyline, Sorafenib, Diclofenac, Estradiol and Dexamethasone. Among these 9 drugs, the targets of 2 drugs (Testosterone and Sorafenib) showed higher topological significance in all 7 topological parameters (For eg. target proteins AR and RAF1 associated with the drugs Testosterone and Sorafenib showed significant values in degree, betweenness, centroid, closeness, eccentricity, radiality and stress categories, showed in green bold face in Fig. 4A). Therefore, 2 drugs (Testosterone and Sorafenib) among the 9 primary repositioning candidates were selected as significant repositioning candidates. Fig. 4A gives the results of the Top-down approach.

3.3.2. Bottom-up approach

The Bottom-up approach is very similar to the Top-down approach, the only difference being its direction. The Bottom-up approach goes in the reverse direction than that of the Top-down approach. In the Bottom-up approach, first we selected the hub proteins in the PPIN based on each of the 7 topological parameters (Fig. 4B). 72 drugs associated with these hub proteins were then selected. Subsequently, we analysed degree of these 72 drugs in the IDTN and the highest degree was found to be 15. Other topological

A Top-down approach:

degree in DTN	top drugs	DTN connections	targets	degree	betweenness	centroid	closeness	eccentricity	radiality	stress
19	Halothane		AR	65	50372.089	-68	2.78E-04	0.125	10.383	508100
16	Propofol		ALB	38	37001.111	-672	2.34E-04	0.112	9.897	238714
15	Testosterone		RAF1	43	26208.007	-273	2.64E-04	0.125	10.249	265320
15	Olanzapine		PDGFRB	23	4844.071	-605	2.42E-04	0.125	9.993	56064
14	Amitriptyline		NTRK1	19	4213.636	-642	2.37E-04	0.125	9.939	44160
14	Sorafenib		FGFR1	18	9946.996	-682	2.35E-04	0.125	9.909	90872
14	Diclofenac		ANXA1	9	1913.184	-760	2.34E-04	0.125	9.895	18778
14	Estradiol		FLT1	15	4487.421	-762	2.31E-04	0.125	9.852	54522
14	Dexamethasone		ALOX5	3	100.424	-1104	2.14E-04	0.125	9.603	1854
			SHBG	11	9948.878	-1004	2.11E-04	0.125	9.564	59862

B Bottom-up approach:

degree	betweenness	centroid	closeness	eccentricity	radiality	stress	targets	DTN connections	targeting drugs	degree in DTN
53	70569.398	-230	2.66E-04	0.125	10.266	611058	CALM1		Testosterone	15
65	50372.089	-68	2.78E-04	0.125	10.383	508100	AR		Nicardipine	13
72	62209.913	-35	2.80E-04	0.125	10.410	605848	ESR1		Nifedipine	13
83	69913.509	-20	2.83E-04	0.125	10.433	752828	EGFR		Lidocaine	11
58	44854.984	-289	2.60E-04	0.125	10.209	412212	FYN		Dasatinib	11
78	63427.261	-24	2.81E-04	0.125	10.419	634432	SRC		Melatonin	10
44	35629.262	-157	2.72E-04	0.125	10.334	351792	ABL1		Diethylstilbestrol	10
43	26208.007	-273	2.64E-04	0.125	10.249	265320	RAF1		Erlotinib	10
5	814.894	-1184	1.98E-04	0.143	9.337	7754	FCGR3A		Imatinib	12
7	887.888	-1002	2.11E-04	0.143	9.558	8770	IL2RA		Sorafenib	14
5	1949.632	-1066	2.14E-04	0.143	9.609	16028	IDE		Aldesleukin	6
27	15807.493	-524	2.45E-04	0.143	10.039	162524	INSR		Insulin, porcine	5
3	13745.857	-1292	1.74E-04	0.143	8.819	96058	HLA-DQB1		Etanercept	4
13	8754.830	-859	2.17E-04	0.143	9.652	62262	CTSD		Trastuzumab	4

Fig. 4. A) Results obtained using the Top-down approach. The significant repositioning candidate drugs are coloured red and bold faced. Their degree in the IDTN is also coloured red and bold faced. Significant targets of these drugs are coloured pink and bold faced. Significant scores of the target proteins are coloured green and bold faced. B) Results obtained using the Bottom-up approach. The significant repositioning targets are coloured red and bold faced. Their degree in the IDTN is also coloured red and bold faced. Significant targets of these drugs are coloured pink and bold faced. Significant scores of the target proteins are coloured green and bold faced. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
On-target ratio (OTR) of known PD-related drugs and nine repositioning candidates.

PD-drugs (D_{PD})	T_{PD}	T_{real}	OTR	Primary repositioned-drugs for PD	T_{PD}	T_{real}	OTR
Rivastigmine	4	4	1	Halothane	19	24	0.79
Carbinoxamine	7	8	0.87	Diethylstilbestrol[b]	10	13	0.77
Ethopropazine	3	4	0.75	Aldesleukin	6	8	0.75
Selegiline	9	12	0.75	Propofol	16	22	0.73
Rasagiline	2	3	0.67	Erlotinib[b]	10	14	0.71
Orphenadrine	6	10	0.6	Lidocaine[b]	11	16	0.69
Diphenhydramine	6	11	0.55	Dasatinib[b]	11	18	0.62
Morphine	7	13	0.54	Nifedipine[b]	13	22	0.59
Tolcapone	1	2	0.5	Testosterone[a,b]	15	26	0.58
Progabide	1	2	0.5	Sorafenib[a]	14	26	0.54
Benzatropine	2	5	0.4	Dexamethasone	14	26	0.54
Ropinirole	7	17	0.4	Nicardipine[b]	13	24	0.54
Rotigotine	4	10	0.4	Melatonin[b]	10	20	0.5
Droxidopa	5	13	0.38	Imatinib	12	24	0.5
Bromocriptine	8	21	0.38	Diclofenac	14	29	0.48
Cabergoline	6	16	0.37	Estradiol	14	30	0.47
Lisuride	6	16	0.37	Olanzapine	15	34	0.44
Sulpiride	1	3	0.34	Amitriptyline	14	33	0.43
Entacapone	1	3	0.34	Insulin, porcine	5	15	0.34
Atropine	2	6	0.34	Trastuzumab	4	14	0.28
Pramipexole	5	16	0.3	Etanercept	4	15	0.27
NADH	44	153	0.29		**Average OTR=**		**0.55**
Levodopa	3	11	0.28				
Apomorphine	4	15	0.27				
Lipoic acid	1	4	0.25				
Hyoscyamine	1	4	0.25				
Amantadine	2	8	0.25	**Final repositioned-drugs for PD**	**T_{PD}**	**T_{real}**	**OTR**
Procyclidine	1	4	0.25	Diethylstilbestrol	10	13	0.77
Trihexyphenidyl	1	5	0.2	Erlotinib	10	14	0.71
Biperiden	1	5	0.2	Lidocaine	11	16	0.69
Metixene	1	5	0.2	Dasatinib	11	18	0.62
Pergolide	2	19	0.1	Nifedipine	13	22	0.59
Carbidopa	0	1	0	Testosterone	15	26	0.58
Cycrimine	0	1	0	Sorafenib	14	26	0.54
Bromodiphenhydramine	0	3	0	Nicardipine	13	24	0.54
Benztropine	0	5	0	Melatonin	10	20	0.5
	Average OTR=		**0.36**		**Average OTR=**		**0.61**

[a] Drugs proposed as significant repositioning candidates based on top-down approach.
[b] Drugs proposed as significant repositioning candidates based on Bottom-up approach.

parameters were also considered and finally we selected 14 drugs (Testosterone, Nicardipine, Nifedipine, Lidocaine, Dasatinib, Melatonin, Diethylstilbestrol, Erlotinib, Imatinib, Sorafenib, Aldesleukin, Insulin porcine, Etanercept and Transtuzumab) which were associated with the topologically significant hub proteins. Out of these 14 drugs, 8 drugs showed higher degree value (≥ 10) and their target proteins (CALM1, AR, ESR1, EGFR, SRC) showed higher topological significance in 6 topological categories (except eccentricity) (Fig. 4B). Thus, 8 drugs (Testosterone, Nicardipine, Nifedipine, Lidocaine, Dasatinib, Melatonin, Diethylstilbestrol and Erlotinib) were selected as significant repositioning candidates. Fig. 4B gives the results of the Bottom-up approach.

Interestingly, Testosterone was the only drug which showed significant results in both Top-down and Bottom-up approaches. Together the Top-down (2 significant repositioning candidates) and Bottom-up approach (8 significant repositioning candidates) gave us 9 significant repositioning candidates for PD.

3.4. Efficiency of repositioning candidates

In order to find out the efficiency of the repositioning candidates we introduced a parameter called the On-target ratio (OTR). OTR is the ratio of the number of PD-specific targets (i.e., in G_{final}) of a drug (T_{PD}) in DTN to total number of interactions of that drug (T_{real}) in DrugBank. OTR ranges from 0 to 1. Thus high OTR (close to 1) indicates higher efficiency of that drug for a particular disease. Table 2 shows the OTR values of D_{PD} and our final repositioning drugs. We observed that the average OTR value of 9 repositioning drugs was much higher than that of the PD-specific drugs (0.61 vs 0.37). Hence these 9 drugs: Diethylstilbestrol, Erlotinib, Lidocaine, Dasatinib, Nifedipine, Testosterone, Sorafenib, Nicardipine and Melatonin were proposed as the most significant repositioning candidates for PD in our study.

Table 3 gives the classes, indications and structures of these 9 repositioning candidate drugs. These drugs have already been known to be associated with various diseases other than PD. However, here we propose these 9 drugs to be most significant repositioning candidates for PD.

4. Conclusion

In our study we have developed a bidirectional drug repositioning method to find out new ways of using the existing drugs for Parkinson's disease. Our method takes into account of both Top-down and bottom-up approaches. In the Top-down approach, significance of nodes in the IDTN leads us to the PPIN. In the Bottom-up approach, the significance of nodes in the PPIN leads to the IDTN. Several topological parameters were used to find out the most significant repositioning drugs in the networks. 9 most significant repositioning candidates viz., Diethylstilbestrol, Erlotinib, Lidocaine, Dasatinib, Nifedipine, Melatonin, Nicardipin, Sorafenib and Testosterone were proposed in our study. Interestingly the average OTR of these repositioned drugs were quite higher than that of the PD specific drugs. To our knowledge, this is the first drug

Table 3
Classes, indications and structures of the repositioning drugs of PD.

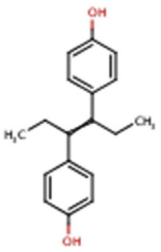
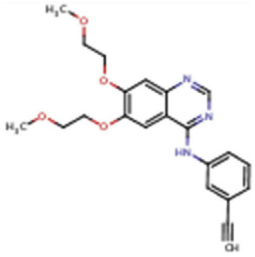
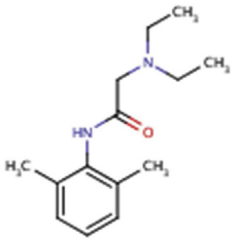
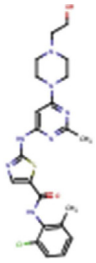
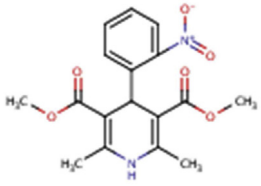
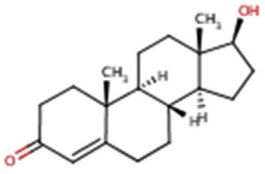
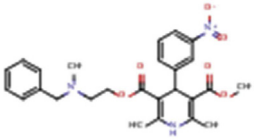
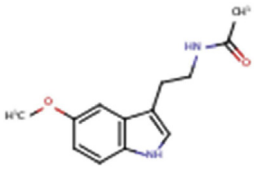
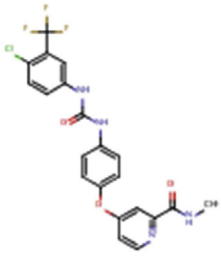
Drug name DrugBank ID	Classes	Indication	Structure
Diethylstilbestrol DB00255	Stilbenes	Prostate cancer	
Erlotinib DB00530	Quinazolines	Metastatic non-small cell lung cancer	
Lidocaine DB00281	Acetanilides, steroids and steroid derivatives	Anesthesia	
Dasatinib DB01254	Piperazines, benzene and derivatives	Chronic myeloid leukemia	
Nifedipine DB01115	Nitrobenzenes	Vasospastic angina, chronic stable angina, hypertension.	
Testosterone DB00624	Steroids and steroid derivatives	Hormone replacement, congenital or acquired hypogonadism, hypogonadism associated with HIV infection. breast cancer	
Nicardipine DB00622	Pyridines and derivatives	Chronic stable angina and for the treatment of hypertension	

Table 3 (*continued*)

Drug name DrugBank ID	Classes	Indication	Structure
Melatonin DB01065	Indoles and derivatives	Insomnia, circadian rhytm disorders, autism, and other central nervous system disorders	
Sorafenib DB00398	Ethers	Hepatocellular carcinoma and advanced renal cell carcinoma	

repositioning study for PD. Our study may help in finding drugs known to work in other diseases to treat PD as well.

Conflict of interest

Authors do not have any conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2014.12.101.

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