Biochemical and Biophysical Research Communications xxx (2015) 1–8

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

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

Hindol Rakshit [a, 1], Paulami Chatterjee [b, 1], Debjani Roy [b, *]

[a] Department of Information Engineering, Computer Science and Mathematics, University of L'Aquila, 67100, Italy
[b] Department of Biophysics, Bose Institute, Acharya J.C. Bose Centenary Building, P-1/12 C.I.T Scheme VII M, Kolkata 700054, India

ARTICLE INFO

Article history:
Received 17 December 2014
Available online xxx

Keywords:
Parkinson's disease
Drug repositioning
Indication-drug-target network
Protein–protein interaction network
Topological significance

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.

* Corresponding author.
E-mail addresses: hindol.iserc@gmail.com (H. Rakshit), chatterjee_paulami@yahoo.co.in (P. Chatterjee), roydebjani13@gmail.com (D. Roy).

[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.bbrc.2014.12.101
0006-291X/

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.

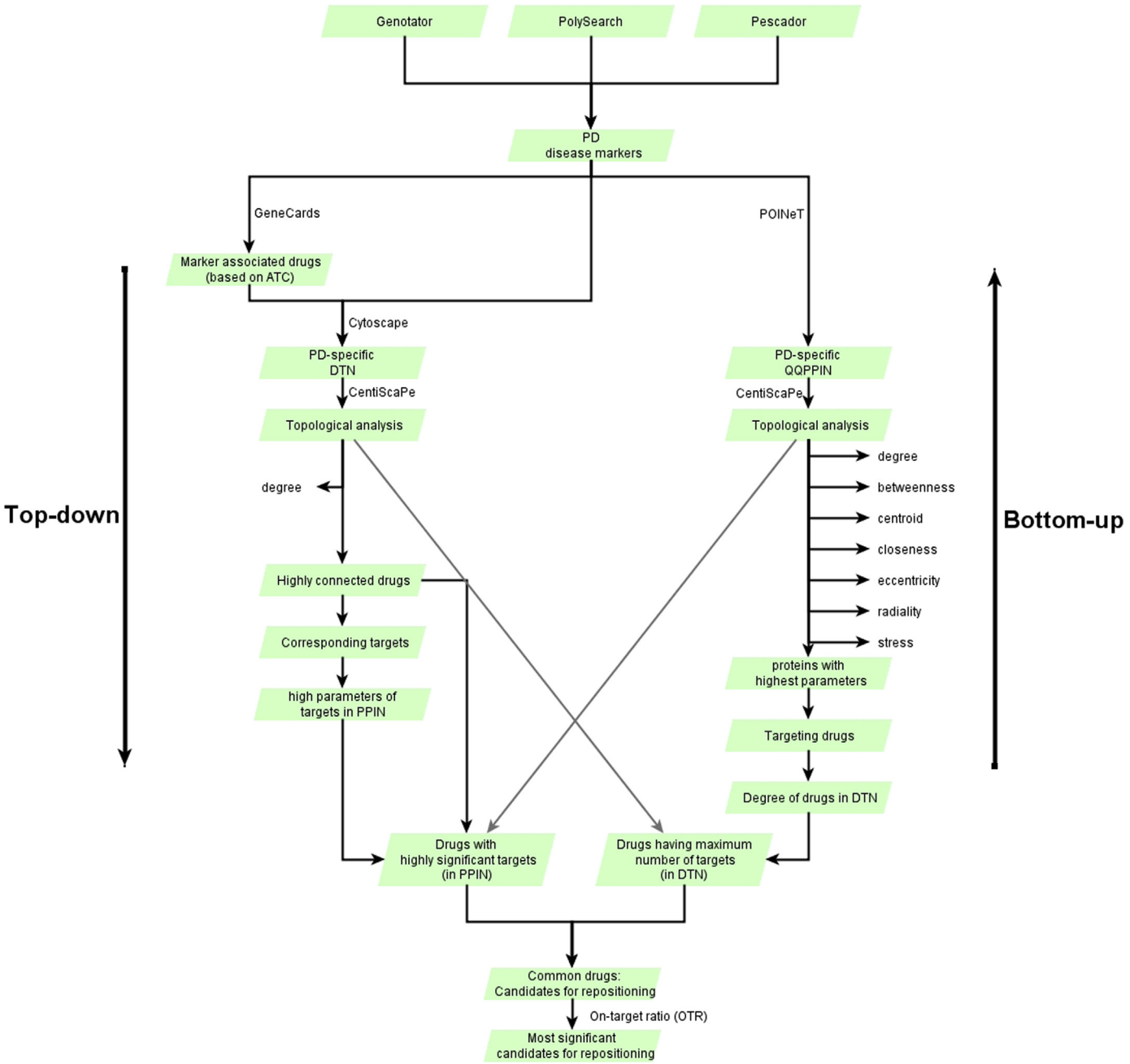

Fig. 1. Work flow of our study.

Please cite this article in press as: H. Rakshit, et al., A bidirectional drug repositioning approach for Parkinson's disease through network-based inference, Biochemical and Biophysical Research Communications (2015), http://dx.doi.org/10.1016/j.bbrc.2014.12.101