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Prediction of Disease-associated Genes by advanced Random Walk with Restart on Multiplex and Heterogeneous Biological Networks

Alberto VALDEOLIVAS^{1,2}, Elisabeth REMY¹, Laurent TICHIT¹, Gaëlle ODELIN² Claire NAVARRO², Sophie PERRIN², Pierre CAU³, Nicolas LEVY³ and Anaïs BAUDOT¹

¹ Aix-Marseille Université, CNRS, Centrale Marseille, I2M UMR 7373, Marseille, France.

² ProGeLife, 8 Rue Sainte Barbe 13001, Marseille, France.

³ Aix-Marseille Université, INSERM, UMR_S910, Faculté de Médecine, France.

Corresponding author: alberto.valdeolivas@etu.univ-amu.fr, anais.baudot@univ-amu.fr

Abstract *Rare monogenic diseases globally affect millions of persons, but many causative genes remain to be discovered. Several computational approaches have been developed to predict disease-associated genes. Guilt-by-association strategies on protein interaction networks, in particular, postulate that proteins lying in a close network vicinity are functionally-related and implicated in similar phenotypes.*

However, current network approaches are limited as they do not exploit the richness of biological networks, which are both multiplex (i.e., containing different layers of physical and functional interactions between genes and proteins), and heterogeneous (i.e., containing both interactions between genes/proteins, and interactions between diseases). In the present study, we extended the Random Walk with Restart algorithm to leverage these complex biological networks.

We compared our algorithm to classical random walks thanks to a leave-one-out strategy. The Random Walk with Restart on multiplex and heterogeneous networks takes advantage of data pluralism and shows increased performances to predict known disease-associated genes. We finally applied it to predict candidate genes for the Wiedemann-Rautenstrauch Syndrome.

Keywords Random Walks with Restart, Biological Networks, Multiplex and Heterogeneous Networks, Disease-Gene Prioritization.

1 Introduction

Rare monogenic diseases are often opposed to common diseases, but they jointly affect millions of persons. Overall, the causative gene(s) are often unknown, many patients remain undiagnosed, and no treatment exists for most of them. The disease phenotypes are resulting not from perturbations of isolated genes or proteins, but of complex networks of molecular interactions [1,2,3]. Proteins, for instance, do not act in isolation, but rather interact with each other to perform their functions in signalling pathways or metabolic reactions. Thanks to the scaling of the experimental techniques allowing interaction discovery, recent years have witnessed the accumulation of interaction datasets. For instance, protein-protein interactions (PPI) are nowadays screened at the proteome scale revealing thousands of physical interactions between proteins. Interaction data are commonly represented as networks, in which the nodes correspond to the genes or proteins, and the edges to their interactions.

In this context, network-mining approaches are applied to study human diseases, and in particular rare monogenic diseases. The rationale underlying these network approaches for human diseases is the clustering of proteins participating to the same cellular functions or biological processes in close network vicinity. Consequently, mutated genes coding for network-related proteins will lead to the same or similar phenotypes [4]. Following this idea, the mapping of the human protein-protein interactome network, about 10 years ago, was used to reveal new disease-associated genes, or allowed prioritizing candidate disease genes [5,6,7]. It also unveiled unsuspected interactions between disease-causing proteins, such as between proteins coded by genes mutated in ataxias [8]. More globally, interaction networks can also help deciphering the etiology and physiopathology of diseases [3], and their comorbidity relationships through their distances in molecular networks [9].

Among the various network-based study of human genetic diseases, Random Walk with Restart (RWR) appears as one of the state-of-the-art guilt-by-association approaches to predict new candidate disease genes. It was initially applied to explore the surroundings of disease-associated protein *seed(s)* in a PPI network. Every

protein in the global network is ranked according to its affinity to the seed(s), thereby allowing the prioritization of new candidate disease proteins [10]. The RWR algorithm was then extended, in particular to leverage phenotypic information [11,12,13,14]. For instance, Li and Patra RWR algorithm [11] considers jointly a PPI network and a network of phenotypic similarities between diseases. The two networks are connected by bipartite protein-disease associations, and form a heterogeneous network, i.e. a network containing nodes and edges of different nature connected by bipartite associations.

However, a common feature and limitation of these approaches is that they ignore the rich variety of information on physical and functional relationships between genes and proteins. Indeed, not only PPI are nowadays described on a large-scale: affinity purification followed by mass-spectrometry experiments inform on the *in vivo* molecular complexes, pathways interaction data are cured and stored in dedicated databases. In addition, functional interactions can be derived, for instance by constructing a co-expression network from transcriptomics expression data. Overall, the exploitation of this diversity of interaction data is lagging behind.

Sets of networks sharing the same nodes, but in which edges belong to different categories or represent interactions of different nature, are known as multiplex (aka multi-layer or multi-slice) networks [15]. In a biological multiplex network, each layer contains a different category of physical and functional interactions between genes or proteins. The combination of the different interaction sources, each having its own features and bias, provides a complementary view on genes and protein cellular functioning.

We present here the extension of the RWR algorithm to multiplex and heterogeneous biological networks (RWR-MH). We demonstrate the increased performance of this algorithm when compared with classical and current RWR approaches. Finally, as a real-case biological example, we applied the RWR-MH algorithm to predict candidate genes for the Wiedemann-Rautenstrauch syndrome (WRS), whose responsible gene(s) remain unknown.

2 Methods

We constructed a multiplex network as described in [16], but updated from downloads on November 2016 (Tab 1). The multiplex network is composed of 3 layers of physical and functional interactions between genes and proteins: protein-protein interactions (PPI), Pathway interactions extracted from pathway databases and Co-Expression interactions derived from RNA-seq expression data. The network nodes correspond equally to genes or proteins.

Additionally, we built a disease-disease similarity network, in which the edges between 2 diseases correspond to significant phenotypic similarities. Briefly, we retrieved diseases and their associated phenotypes from the Human Phenotype Ontology (HPO) [17]. We then computed the phenotype similarity between diseases, by measuring the relative information content of the common phenotypes of every disease pair. We thereby assumed that rare phenotypes in the HPO database are more informative than frequent ones, as proposed by [18]. Finally, the disease-disease similarity network is constructed by linking every disease to its 5 most similar diseases according to their phenotype similarity scores, as proposed in [11].

The multiplex and heterogeneous network is constructed by linking every layer of the multiplex with the disease-disease similarity network using known gene-disease bipartite associations extracted from OMIM [19].

Network	Number of nodes	Number of edges
PPI	12 621	66 971
Pathways	10 534	254 766
Co-expression	10 458	1 337 347
Disease-disease similarity	6 947	28 246

Tab. 1. Size of the networks used in this work.

We extended the RWR algorithm to consider multiplex and heterogeneous networks (RWR-MH). In a nutshell, starting from initial seed node(s), the RWR progresses following the graph topology, with a non-zero probability to jump back to the initial seed node(s) at each step. After a sufficiently large number of iterations, RWR reaches a stationary state. In this stationary state, each nodes is associated to a score reflecting its proximity or pertinence with respect to the initial seed(s). Our extended RWR-MH algorithm has the capacity to explore one network layer, but also to jump between the different layers of the multiplex, because the same

nodes are present in the different layers. In addition, it can jump to the disease-disease similarity network thanks to the gene-disease bipartite associations. At every time, the walk can return to the initial protein and/or disease seed node(s), with a defined probability that we set to 0.7, as in previous studies [10,11,12].

We applied a leave-one-out cross-validation (LOOCV) strategy to compare RWR-MH with other RWR approaches. For every disease in OMIM [19] associated to 2 genes or more, each disease-associated gene is removed one-by-one (we will later refer to this removed gene as the left-out gene). The remaining disease-associated genes and the disease itself are used as seed nodes, and the RWR algorithms are applied. The Cumulative Distribution Functions (CDFs) are used to evaluate and compare the performances of the different approaches. They display the percentage of left-out genes that are ranked within the top k genes.

3 Results

3.1 RWR-MH outperforms current RWR approaches

We first compared different algorithms: i) the classical RWR on a monoplex PPI network, ii) the RWR on a heterogeneous network (built with the PPI and the disease-disease similarity network, RWR-H, as proposed by [11]), iii) the RWR on a multiplex network (composed of 3 layers, namely PPI, pathways and co-expression, RWR-M), and finally iv) the RWR on the multiplex-heterogeneous network (RWR-MH).

We applied a LOOCV strategy to evaluate the performances of the different RWR algorithms (Methods) for the prediction of known disease-associated genes (Fig 1). The multiplex RWR-M shows a superior performance than the classical RWR on a monoplex network. It is however comparable to the heterogeneous RWR-H. The multiplex and heterogeneous RWR-MH is remarkably better, since more than 45% of the left-out genes are ranked within the top 20.

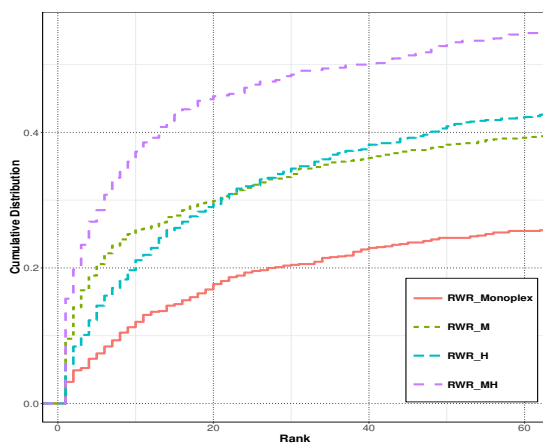


Fig. 1. Cumulative Distribution Functions of the rank of each left-out gene retrieved by the LOOCV strategy. The algorithms are the classical RWR applied to the PPI monoplex network, the RWR-M applied to the 3-layer multiplex network, the RWR-H applied to the heterogeneous network built from the PPI and the disease-disease similarity networks, and the RWR-MH applied to the multiplex-heterogeneous network.

3.2 RWR-MH prediction of candidate genes for the Wiedemann-Rautenstrauch Syndrome

The Wiedemann-Rautenstrauch Syndrome (WRS; MIM code: 264090), also called neonatal progeroid syndrome, is a disorder characterized by intrauterine growth retardation with subsequent failure to thrive and short stature [20]. In addition, patients display a progeroid appearance at birth and during the infancy, decreased subcutaneous fat, hypotrichosis and macrocephaly [21]. Only a few case reports have been documented, and no gene(s) has been described as causative of the syndrome yet.

To illustrate our approach, we applied our RWR-MH algorithm using as seed the WRS disease node. For visualization purposes, we displayed only the top 25 ranked diseases and top 25 ranked genes scored by the RWR-MH algorithm (Fig 2).

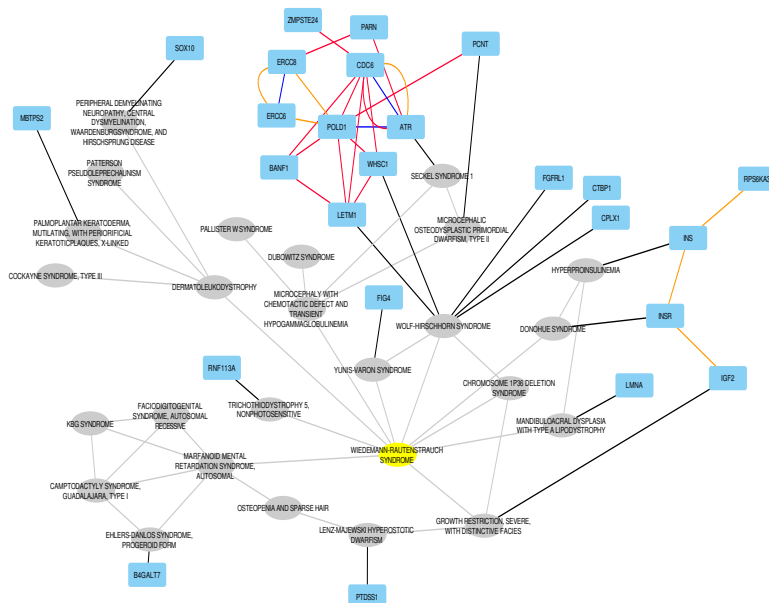


Fig. 2. Multiplex and Heterogeneous Network linking the top 25 genes and top 25 diseases obtained when the RWR-MH algorithm is applied using WRS as seed (yellow node). Grey elliptical nodes represent diseases, while turquoise rectangles represent genes. Black edges account for the bipartite gene-disease associations; Grey edges are the similarity links in the disease-disease similarity network; Blue edges correspond to PPI interactions; Red edges represent co-expression relationships; Orange edges represent pathway interactions.

We predicted the top scored genes as top candidates for being involved in WRS. Many of them, such as *FIG4*, *RNF113A* or *LMNA*, are implicated in diseases directly connected to WRS from phenotypic similarities. For instance, mutations in *LMNA* are responsible for Hutchinson-Gilford progeria syndrome (HGPS; MIM code: 176670) and other premature aging syndromes such as Mandibuloacral Dysplasia with type A Lipodystrophy (MAD-A; MIM code: 248370). However, no mutations were found targeting *LMNA* sequence by gene sequencing analyses of WRS patients [21,22]. Additionally, the RWR-MH algorithm evidenced *ZMPSTE24*, which is known to be responsible of severe progeroid syndromes such as restrictive dermopathy (RD, MIM code: 275210) [23]. This peptidase acts during the post-translation modifications of the prelamin A, coded by *LMNA*, to undergo the complete maturation to lamin A. The direct interaction between the products of *LMNA* and *ZMPSTE24* is missing in the databases we used to construct our multiplex network. The *ZMPSTE24* nodes is however retrieved through different trajectories in the random walk. Once again, no mutations were found in the *ZMPSTE24* gene among the 5 WRS patients [22].

An interesting result is the small subnetwork composed of the genes *IGF2*, *INS*, *INSR* and *RPS6KA3*, which all participate to the insulin pathway. We retrieved these genes as top candidates due to their associations with two different diseases linked to WRS. This pathway is suspected to play a role in WRS [22]. Similarly, a cluster of proteins related to the cell cycle and DNA repair is connected to WRS through the Wolf-Hirschhorn syndrome (MIM code: 194190). DNA repair defects are also suspected to be involved in WRS [22]. The next step will be to validate these predictions, for instance using exome-sequencing data. Overall, our extended guilt-by-association RWR-MH algorithm could be integrated in analysis pipelines to help predicting candidate genes for rare diseases.

4 Discussion

Random Walk with Restart (RWR) is one of the state-of-the-art guilt-by-association approaches to prioritize candidate disease genes. We here extended the classical RWR algorithm in order to navigate multiplex and heterogeneous networks. We also demonstrated the increased performance of the RWR multiplex and heterogeneous strategy by leave-one-out cross validations. This improvement is due to the ability of our algorithm to extract and integrate the information from many interaction sources. Other types of networks could be integrated in the future, for instance to include interactions with non-coding RNAs. In addition, it would be interesting to explore the impact on the results of different disease-disease network topologies, i.e. taking a different criteria to build the disease-disease phenotype similarity network.

RWR has been mainly employed in biology to predict disease-associated genes [10,11,12,14,13]. But it has also been applied to address other biological problems, such as the prediction of drug-target potential interactions [24], the identification of clusters from PPI networks [25], or the prediction of adverse drug reactions [26]. Multiplex approaches are likely to boost the results of all these different applications, and could also be adapted to study cellular functioning as a whole.

The next step will be to resolve the degree bias of the algorithm. Indeed, RWR algorithms and other network propagation methods are biased towards networks hubs [27]. Therefore, poorly-connected and not well-characterized proteins, which can also be related to diseases, are hard to detect. Biased random walks can tackle this issue by relating the probability of transition to the degree of the nodes [28].

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