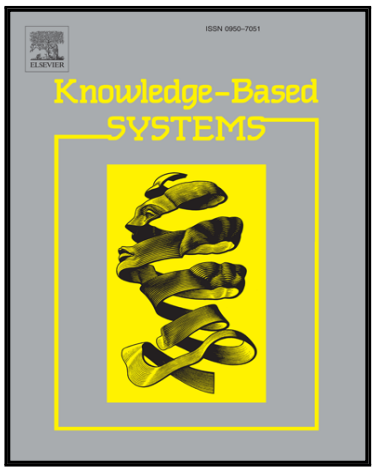

RESKO: Repositioning drugs by using side effects and knowledge from ontologies

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RESKO: Repositioning drugs by using side effects and knowledge from ontologies

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Abstract

The objective of drug repositioning is to apply existing drugs to different diseases or medical conditions than the original target, and thus alleviate to a certain extent the time and cost expended in drug development. Our system RESKO, REpositioning drugs using Side Effects and Knowledge from Ontologies, identifies drugs with similar side-effects which are potential candidates for use elsewhere, the supposition is that similar side-effects may be caused by drugs targeting similar proteins and pathways. RESKO, integrates drug chemical data, protein interaction and ontological knowledge. The novel aspects of our system include a high level of biological knowledge through the use of pathway and biological ontology integration. This provides a explanation facility lacking in most of the existing methods and improves the repositioning process. We evaluate the shared side effects from the eight conventional Alzheimer drugs, from which sixty-seven candidate drugs based on a side-effect commonality were identified. The top 25 drugs on the list were further investigated in depth for their suitability to be repositioned, the literature revealed that many of the candidate drugs appear to have been trialed for Alzheimer's disease. Thus verifying the accuracy of our system, we also compare our technique with several competing systems found in the literature.

Keywords: side-effects; graph theory; pattern matching; protein targets; ontologies

1. Introduction

In this paper we demonstrate how adverse drug side-effects can be used to identify potential candidates for drug repositioning for a variety of diseases. Drug re-purposing or repositioning involves using existing pharmaceutical products for diseases or problems they were not specifically designed for. There are many advantages since off-the-shelf drugs have undergone extensive testing and their toxicological properties are well known, therefore the costs are greatly reduced and also time to product delivery [31]. Thus it is more economical to re-purpose an existing drug than develop one from scratch [16]. Difficulties in drug development arise because diseases are often complex with multi-factorial components such as interactions between genes, proteins and the environment [7]. Furthermore, drugs that are highly selective in terms of their targets are very rare. Many patients when taking a drug will experience unwanted side-effects as the medication may also also interact to varying degrees with non-target proteins [52]. However, this feature can be used to search for drugs with similar side-effects that might target the defective biological functions more effectively than conventional drugs. Since there is wealth of freely available drug and protein databases, drug repositioning is an ideal application area for knowledge based systems and computational statistics.

However, not all of the drug repositioning discoveries are through computational intelligence techniques. Interestingly, there are many examples where unanticipated side-effects have proven to be beneficial to patients suffering from unrelated problems to the original purpose of the drug thus allowing the drugs to be re-deployed [53]. The most often cited example is Sildenafil, a drug developed by Pfizer which was intended to treat heart problems by allowing better blood flow. It was discovered to have a particular side-effect on the male participants, it was later marketed as Viagra, the drug now has annual sales in excess of $1.6 Billion [1]. Other notable drugs such as the infamous Thalidomide that caused birth defects in the 1950s, has been redeployed to treat leprosy and multiple myeloma [45].

A deeper understanding of the causes of disease is necessary, in particular knowledge of the genetic differences between individuals will eventually lead to improved treatments [40]. This has only recently been made possible by the development of advanced genomic and proteomic techniques which are able to provide detailed and accurate data on individual cellular processes [12]. We are

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