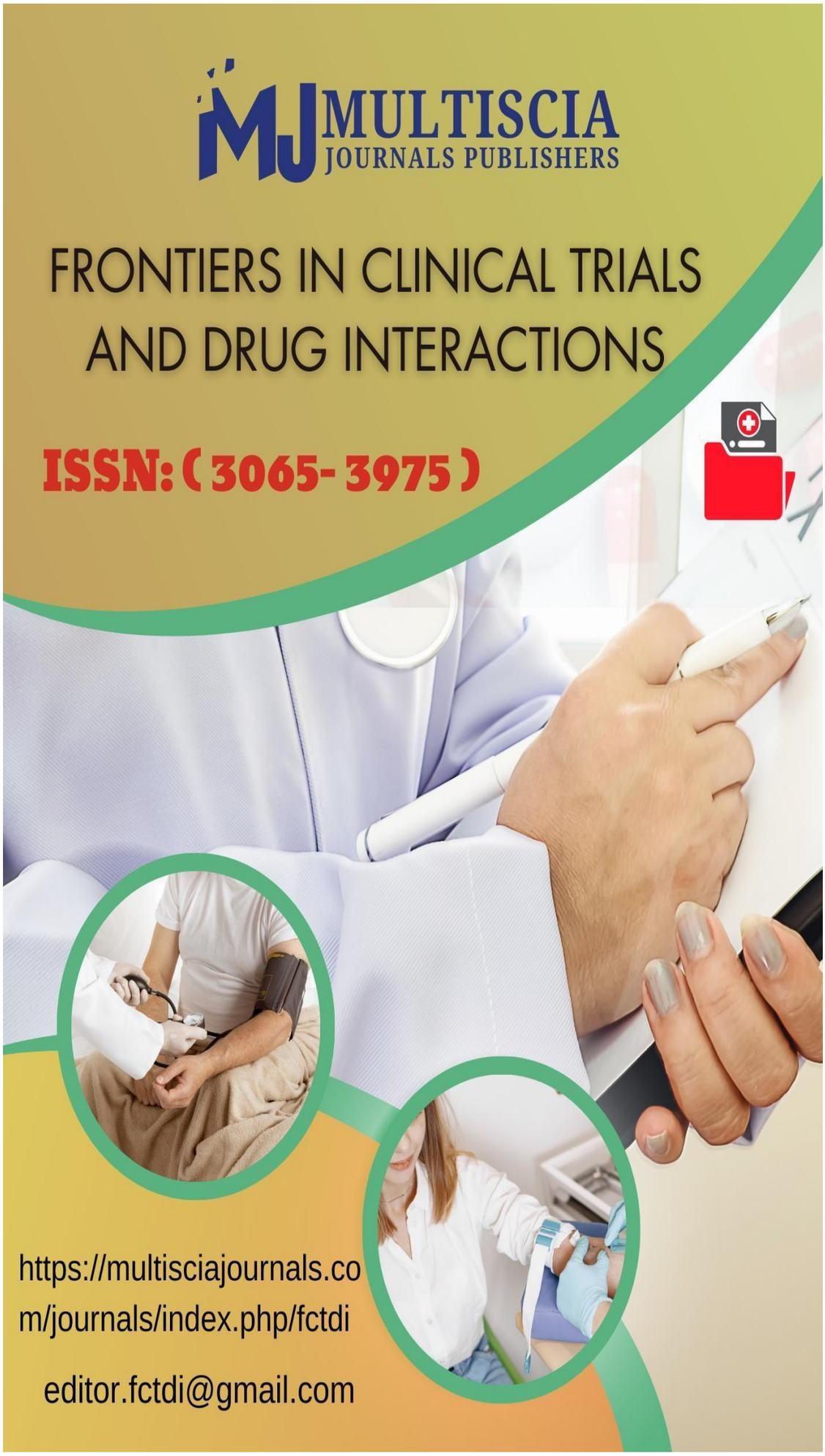
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Drug-drug interactions in informatics

Martin
Department of Clinical Trials and Drug Interactions

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Abstract

Public health is increasingly at risk from drug-drug interactions (DDIs). According to recent estimates, DDIs result in approximately 74,000 ER visits and 195,000 hospital admissions annually in the United States. Phase IV clinical trials and post-marketing surveillance are examples of current DDI discovery methods that are inadequate for identifying many DDIs and do not notify the public of potentially harmful DDIs prior to a drug's release onto the market. Modern statistical and computational techniques have been used to the DDI problem in recent work. Here, we examine recent advancements that cover a variety of informatics techniques in this field, from building databases for effective searching of known DDIs to predicting new DDIs using information from electronic medical records, adverse event reports, scientific abstracts, and other sources. We also discuss the reasons for the difficulty of detecting DDIs and the prospects for informatics-based methods of DDI discovery.

Drug–drug interactions: incidence and impact

Drug-drug interactions (DDIs) account for about 0.054% of ER visits, 0.57% of hospital admissions, and 0.12% of rehospitalizations, according to a 2007 meta-analysis of 23 clinical studies from around the globe [1]. In the United States alone, there are 34.1 million hospital discharges [3] and 136.1 million ER visits [2] year. If these figures are accurate, Americans have DDI incidents severe enough to require almost 74,000 ER visits annually, and hospitals admit approximately 195,000 patients annually due to DDIs. It should come as no surprise that DDIs also lead to longer hospital stays and higher costs [4].

As more people use numerous medications at once, we should anticipate a rise in the incidence of DDI. The Centers for Disease Control (CDC) report that between 1988 and 1994, 39.1% of Americans took at least one prescription medication over the previous 30 days; by 2007 and 2010, that number had risen to 47.5%. In the same time frame, Americans who took three or more prescription medications grew from 11.8% to 20.8%, while those who took five or more medications went from 4.0% to 10.1% (Figure 1a) [5]. The elderly are more prone to polypharmacy, which increases their vulnerability to DDIs (Figure 1b). According to the 2007 study mentioned above, DDIs resulted in 4.8% of hospital admissions among the elderly, which increased their risk by about 8.5 times compared to the general population.

Informatics-based methods for researching DDIs have recently flourished due to the increased availability of vast volumes of drug-related data. Researchers can more readily create comparative, data-driven methods to identify, anticipate, and explain drug interactions thanks to increased access to extensive databases of electronic medical records (EMRs), scientific publications, population-based reports of adverse events, drug labels, and other sources. Here, we go over the difficulty of researching DDIs, the range of informatics techniques now in use, and the obstacles that still need to be overcome.

Why DDIs are difficult to study

It is legitimate to wonder why so many DDIs remain undiagnosed for so long, given that many known DDIs involve common drugs like antihypertensives, anti-inflammatories, and anticoagulants (Table 1). DDIs have occasionally resulted to the removal of drugs from the market, although even in these instances, the substances were typically accessible to the general public for years prior to withdrawal [6,7]. The difficulty of identifying DDIs in the clinic, the dose dependence of many DDIs, the nature of the drug approval process, and natural genetic and demographic variation can all cause delays in DDI recognition, even though in vitro laboratory studies, such as DDI assays, can help alert drug manufacturers and the scientific community to the presence of new DDIs.

For instance, it is unrealistic to expect practicing physicians to identify and record the majority of DDIs on their own. It can be challenging to identify whether adverse events are caused by interactions between two or more medications, side effects from a single medication, or worsening of the patient's underlying disease or diseases because patients who take numerous medications frequently have multiple comorbidities. Additionally, doctors may not be able to identify patterns of interactions within their own patient cohorts if there are few patients on a given medication combination, particularly within a single practice or institution. Additionally, certain DDIs are dose-dependent, meaning that unless a patient is administered at the upper end of the permitted range for one or both medications, a DDI may not be detectable.

Furthermore, it is frequently challenging to notice DDIs in a pre-market clinical study setting. Only 1000–3000 people are typically enrolled in phase III clinical trials, which are the final step of research before a medication is put on the market. Few, if any, research participants will have DDI-related symptoms during the study if the test agent interacts with a medication that is not commonly supplied to members of the study population, or if the interaction is mild or uncommon. Therefore, it should come as no surprise that the DDIs that we are aware of are either those that occur between highly frequently given groups of medications or those that produce the most frequent and severe side effects.

Lastly, the effects of many DDIs may be obscured by inherent human variability. We already know that people with specific genetic complements are more susceptible to negative side effects [10] and more sensitive to the effects of some medications [8, 9]. Therefore, we may anticipate that specific genetic subpopulations—such as those with transporter gene alterations or those who are "fast" or "slow" metabolizers—would experience DDIs more frequently. Additionally, we know that a large portion of the variance in dosage requirements for many pharmaceuticals can be explained by demographic variation, which includes differences in age, gender, race/ethnicity, weight, and height, among other things [8,11,12]. Therefore, we might anticipate that these factors would also complicate DDI identification. Many of these challenging circumstances are addressed in publications published by the US Food and Drug Administration (FDA) on a regular basis. Summaries of these articles can be found in [13] and [14].

Why informatics?

Given these difficulties, it is clear that a new paradigm for discovery is required if we are to anticipate and comprehend DDIs on a wide scale. Nowadays, the majority of DDIs are still unintentionally found in clinical settings or during Phase IV clinical trials, which happen after a medication has been put on the market. (This is reflected in a number of the DDIs in Table 1; for instance, the interaction between terfenidine and ketoconazole was initially suggested in a 1990 case report of a single patient in a Maryland hospital who developed tachycardia when taking both medications concurrently.) The scientific community is alerted to potential drug interactions by in vitro and in vivo laboratory investigations [15], and modeling techniques like kinetic models of drug levels inside the body [16,17] advance our knowledge of DDI mechanisms. However, each of these approaches only examines one or a small number of drug combinations at a time.

Approaches in informatics are distinct. Their capacity to handle massive volumes of data simultaneously—using computers to go through and prioritize thousands of possible DDIs—is their greatest asset. They rely on the existence of big data repositories that hold anything from original clinical documentation from EMRs to scholarly articles and structural details about pharmacological compounds. A shifting scientific reality is reflected in informatics techniques. Every day, enormous volumes of laboratory and clinical data pertinent to DDI prediction are already gathered and stored. Despite their volume, these data could be missing or noisy. Therefore, in order to identify DDIs, we need new methods for searching, organizing, and manipulating this data in addition to gathering more of it.

Integrating data sources

Researchers have been able to more accurately identify, forecast, and explain DDIs thanks to a number of new data sources in recent years. These sources, which we outline below and in Table 2, are used in at least one of the papers we review. We have attempted to include data sources that occur in many articles and/or represent the range of DDI-related data that are currently available, even if we are unable to offer an entire list of all the sources that contributed to these papers.

Scientific articles and abstracts

There are already approximately 20 million citations in Medline, the largest database of scholarly publications in the biomedical field in the world, and many more are added every day. Text mining

techniques that aim to comprehend DDIs based on remarks made about medications during biological research are made possible by these records, which comprise the titles, abstracts, and occasionally the entire text of biomedical research papers. The whole Medline database can be downloaded in XML format for home use, and the Entrez Programming Utilities offer simple search and retrieval capabilities for Medline data.

Adverse event reporting systems

As a kind of post-marketing surveillance, several countries keep databases of adverse occurrences related to healthcare through spontaneous reporting systems. Through the FDA Adverse Event Reporting System (FAERS), consumers, pharmaceutical companies, and medical professionals in the United States report adverse events and prescription errors to the government. Other nations, like Canada and Italy, may have different regulations and keep their own databases for reporting adverse events.

Drug information resources

The National Library of Medicine Daily Med website provides the complete text of all prescription and over-the-counter medication labels accessible in the United States. Important details on formulations, adverse effects, and known drug interactions are included on these labels. A comparable site for medications sold in Japan is the Japan Pharmaceutical Information Center (JAPIC).

Gold-standard sets of known interacting drug pairs for DDI detection techniques are frequently created using DrugBank, a database that integrates comprehensive chemical, pharmacological, and pharmaceutical data with sequence, structural, and route information on drug targets [18]. Additionally, it acts as a central store for valuable data regarding drug structure and activity, including Anatomic, Therapeutic, Chemical Classification (ATC) codes [20] and Simplified Molecular Input Line Entry System (SMILES) codes [19]. A comparable resource for all government-approved medications in the United States, Europe, and Japan is the KEGG DRUG database. It contains details about drug interactions with other molecules, target molecules, metabolizing enzymes and transporters, and molecular structure [21].

Important information on medication binding and bioactivity is available in a number of databases. The WOMBAT (World of Molecular Bioactivity) database, which is primarily focused on the pharmaceutical sector, includes information on protein–ligand binding from 15,320 publications that were published in medicinal chemistry journals between 1975 and 2009 [22]. There are 331 872 entries in WOMBAT, which represent 1966 distinct objectives. ChEMBL [23] includes 5200 protein targets and 5.4 million bioactivity data for over a million chemicals. BindingDB [24] includes 910 836 binding data that show interactions between 378 980 small compounds and 6263 protein targets.

PharmGKB is an extensive database that compiles data regarding how genetic diversity affects pharmacological response [25]. PharmGKB produces lexicons of known pharmacological names and synonyms, gene and disease words, and information on genetic pathways with a focus on physicians and researchers. PharmGKB also offers the TWOSIDES database, which is a database of DDI side effects, and the OFFSIDES database, which is an extensive database of medication effects extracted from adverse event reports [26].

Lastly, drug-side-effect relationships that were discovered by text mining from drug packaging inserts are included in the SIDER [27] database. It included data on 4199 side effects, 996 medications, and 100,049 drug-side-effect pairs at the time this review was written.

Electronic medical records

By offering a means of validating predicted DDIs, the availability of raw data from EMRs has significantly aided informatics methods to DDI prediction. However, a member of the study team who is connected to the institution and the institutional review board must typically approve the use of EMR data at a given institution. The primary obstacle to this kind of data is still access, although some academic medical facilities have developed interfaces to their EMRs to support translational research (e.g., STRIDE [28]). Recently, the Informatics for Integrating Biology and the Bedside (i2b2) Center at Partners HealthCare in Boston created publically accessible software enables researchers to use a query tool interface to locate patients of interest from EMRs while protecting patient privacy [29].

Putting it all together

We discovered 20 recent publications that combined these and other data sources to anticipate new DDIs, explain DDI mechanisms, and compile existing knowledge on DDIs into practical databases. There are four primary categories for these articles. The creation and curation of knowledge bases about recognized DDIs is the primary emphasis of the first group. Methods for directly extracting statements regarding DDIs from text are included in the second group. The third and fourth groups focus on using information gleaned from various data sources to forecast new drug interactions. While the fourth group integrates pharmacogenomic or chemoinformatic data from a variety of additional sources, the third group makes predictions using adverse event reports.

publications from the last few years that combined these and other data sources to anticipate new DDIs, explain DDI mechanisms, and compile existing knowledge on DDIs into practical databases. There are four primary categories for these articles. The creation and curation of knowledge bases about recognized DDIs is the primary emphasis of the first group. Methods for directly extracting statements regarding DDIs from text are included in the second group. The third and fourth groups focus on using information gleaned from various data sources to forecast new drug interactions. While the fourth group integrates pharmacogenomic or chemoinformatic data from a variety of additional sources, the third group makes predictions using adverse event reports.

Group 1: building DDI knowledge bases

In order to transform known DDI data into practical tools for academics and physicians, a number of studies reported using a combination of automatic text-mining algorithms and manual curation. These studies show how the data from the other three groups might potentially be used in reality and represent the most practical edge of the informatics field.

Numerous known pharmacokinetic DDIs are mediated by liver cytochrome P450 enzymes (CYPs), which are widely implicated in drug metabolism [30]. (When one medication interferes with the body's capacity to digest, absorb, distribute, or excrete another medication, this is known as a pharmacokinetic DDI.) Preissner et al. searched hundreds of Medline abstracts and other sources for information regarding CYP-related genetic variants and their impact on drug metabolism in order to create SuperCyp [31], a compilation of data about these significant enzymes. Information on 57 CYPs and their interactions with 1170 medications can be found in their database, along with supporting data for each interaction that, when available, includes the research population. Users can explore the 3D structures of the CYPs themselves and investigate how drug co-administration affects CYP-related drug metabolism.

Using a more comprehensive method, Takarabe et al. created a DDI resource that combines pharmacokinetic and pharmacodynamic DDIs [32]. (A pharmacodynamic DDI happens when a drug interacts with another drug's protein target or another protein in the same pathway.) DDIs may be searched at any level of granularity, from the general (interactions between drug classes) to the specific (interactions between individual medications), thanks to the hierarchical network structure of their database. The KEGG DRUG database was then merged with this resource. By looking at medication pairings that share protein targets or are processed by the same enzymes, users can examine over 200,000 known interactions and determine whether others are plausible. It makes appropriate to create separate, disease-specific DDI databases for some medication classes. A wealth of information regarding anticancer medications and their interactions with complementary and alternative therapies—particularly traditional Chinese medicines—used in oncology is available through the OncoRX project [33]. The clinical significance of interactions between antidepressants and anticancer medications was examined by the same authors using their database [34].

Lastly, the clinic already uses a few large-scale DDI datasets. DDI databases are difficult to employ in real-time clinical settings since they usually need to be connected with pre-existing EMR software. A database containing more than 8000 DDIs from seven different sources, including Medline, is part of the SFINX project [35]. To make DDI detection in clinical practice easier, it was recently incorporated with the computerized decision support systems in Finland and Sweden.

Group 2: explicit DDI statement extraction

Manual curation methods are becoming less and less popular as the amount of information about DDIs increases. A few research automated Group 1's manual database curation method by mining medicine labels or the scientific literature for statements concerning known DDIs. All of these

papers were generated as part of the DDI Extraction Challenge held in 2011 by the SEPLN 2011 Satellite Workshop. One outlines a rule-based method for extracting DDIs from unstructured text that finds phrases that explain DDIs by combining pattern matching, syntactic simplification, and shallow parsing. The third study, which won the competition, used an ensemble of various machine learning techniques, while another study used a machine learning-based approach to complete the identical job [36–38].

Group 3: mining adverse event reports

Even if the data is automatically extracted, all of the methods in Groups 1 and 2 rely on information about known DDIs. However, we have seen that a major bottleneck exists in our current paradigm for DDI identification. The final set of articles includes methods for automatically mining adverse event reports, which essentially uses computers to conduct extensive post-marketing surveillance. These methods are interesting because they make it possible to identify DDIs when a Phase IV clinical study would be too expensive or time-consuming, or when the DDI in question is completely unforeseen.

From a corpus of 162 744 adverse event reports from FAERS, Harpaz et al. used association rule mining to find 1167 multi-item adverse drug event associations; an expert identified and validated 4% of those as DDIs [39]. This study marks one of the first attempts to apply association rule mining, a popular data-mining technique that is most frequently utilized in online recommendation systems [40], to biological monitoring. It is predicated on the idea of a "market basket"; for instance, an association rule-mining system may determine that a user is likely to purchase bread if he purchases peanut butter and jelly. In a similar vein, it is possible to determine the probability that an adverse event report that includes two drug names would also mention a specific adverse event.

To find adverse events linked to DDIs, Leone et al. examined data from a database that included all reports of suspected adverse drug reactions from five Italian regions [41]. After searching FAERS records for glucose homeostasis-related side-effect profiles for a year, Tatonetti et al. discovered a unique interaction between paroxetine and pravastatin that raises blood glucose levels in a potentially harmful way [42]. They demonstrated the effectiveness of a two-step method in which researchers use spontaneous reporting databases to forecast novel DDIs and EMRs to validate them. They confirmed their findings using EMR data from Vanderbilt Hospital, Stanford Hospital, and Partners HealthCare. Additionally, these authors created new signal identification techniques to minimize the impact of confounding variables such a patient's age and underlying medical status [26] and to find DDIs in adverse event reports [43].

Group 4: combining pharmacogenomic and chemoinformatic data

The fourth and largest group of papers took the Group 3 approach one step further, attempting to predict novel DDIs based on mechanistic and structural information about the drugs themselves and their interactions with proteins. Although these methods are more difficult to validate than those of Group 3, their advantage lies in the fact that they rely mainly on chemical and bioactivity data from laboratory studies rather than clinical data. As a result, they could potentially be used to predict DDIs before drugs enter the market.

Several of these papers rely on statements from the scientific literature. For example, both Percha *et al.* and Tari *et al.* mined Medline for single sentences containing drug–gene relationships [44,45]. Although their relation extraction approaches differ, in both cases these sentences became raw ‘facts’ that were combined to predict DDIs. In both papers, approximately 80% of predicted DDIs matched those in a gold-standard set from DrugBank.

Duke *et al.* used a hybrid approach in which they first mined the scientific literature for abstracts connecting drug names to CYP enzymes using text analysis and manually curated these abstracts to retrieve relevant gene–drug information [46]. They then used an EMR to restrict their findings to drug combinations that were commonly co-prescribed and found five novel combinations that synergistically increased patient risk of myopathy.

Other papers describe systems that integrate knowledge from a plethora of different sources. The INDI system developed by Gottlieb and colleagues uses a gold-standard set of DDIs from DrugBank and Drugs.com, computes seven distinct drug similarity measures based on chemical, side-effect and target protein similarity data, and then ranks other drug pairs based on how similar they were to known DDIs [47]. Similarly, the Drug Interaction Knowledge Base (DIKB) integrates evidence from retrospective studies, clinical trials, metabolic inhibition identification, metabolic catalysis identification, statements, reviews, and observational reports [48]. Curators manually collect evidence about drugs and drug metabolites and classify this evidence by type and strength. They then apply over 1000 different reasoning strategies to their data and evaluate which strategies are most successful at predicting DDIs. These strategies define the different levels and types of evidence required to infer that a DDI is likely [49].

Finally, Vilar *et al.* used a similarity analysis of drug molecular structures to identify novel DD Is by looking

for drugs that were structurally similar to those involved in known DDIs [50]. Their method had sensitivity of 0.68, specificity of 0.96, and precision of 0.26 against a gold standard of known DDIs from DrugBank.

Concluding remarks

Recognizing, explaining, and ultimately predicting DDIs constitute a huge challenge for medicine and public health. Not only are DDIs incredibly diverse, both in terms of their biological mechanisms and their severity, but many also occur rarely enough, or produce effects unpredictable enough, to go unnoticed through the entire drug approval process. Given the rate at which polypharmacy is increasing in the USA and around the world, we can only expect this problem to worsen over time. Fortunately, it has coincided with a tremendous increase in the availability of drug-related data in scientific texts, EMRs, adverse event reports from hospitals and consumers, and dozens of databases covering drug mechanisms, side effects, and chemistry.

In this environment, informatics approaches that seek to organize the data surrounding DDIs, facilitate data extraction and database curation, and use data creatively to predict novel DDIs are already bearing fruit. The future promises progress in two areas: (i) evaluating DDI predictions clinically and deciding if they merit intervention recommendations to prescribers, and (ii) using DDI knowledge as a way to probe the molecular mechanisms of drug response. DDIs are important not only with respect to improving healthcare but also because they offer a window into the molecular mechanisms by which drugs interact with the body and with each other. Understanding the molecular details of a DDI might therefore help to illuminate the ways in which the drugs and their targets participate in the molecular networks leading to drug response. Such knowledge might be useful for understanding the basic pathophysiology of health and disease and may provide insights useful for the development of new drugs, new drug combinations, or new uses for old drugs (drug repurposing).

Early informatics approaches to DDI prediction provide us with an interesting case study of what we should expect as ‘big data’ enters the healthcare realm. Large-scale algorithmic approaches to DDI prediction enable us to organize and process orders-of-magnitude more data than ever before, but no matter how sophisticated an algorithm is, its results will still be fraught with uncertainty. How do we know that the results we are seeing are not artifacts? How can we ensure that we are focusing our attention on DDIs that are most clinically relevant? How can we confirm or deny our results? We can address some of these questions with increasingly sophisticated statistics, but ultimately even ‘big data’ predictions will still need to be validated in the clinic and laboratory. We envision a paradigm in which broad, data-driven algorithms alert the healthcare community to new evidence of DDIs, EMRs provide an additional layer of support to boost the best predictions to the top, and laboratory experiments serve as the final arbiter, confirming or denying newly predicted DDIs. It looks as if that day is coming soon.

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