Drug interaction networks: an introduction to translational and clinical applications

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Abstract

This article introduces fundamental concepts to guide the analysis and interpretation of drug–target interaction networks. An overview of the generation and integration of interaction networks is followed by key strategies for extracting biologically meaningful information. The article highlights how this information can enable novel translational and clinically motivated applications. Important advances for the discovery of new treatments and for the detection of adverse drug effects are discussed. Examples of applications and findings originating from cardiovascular research are presented. The review ends with a discussion of crucial challenges and opportunities.

Keywords Systems biology • Drug-interaction networks • Adverse drug events • Drug repositioning

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1. Connecting drug–target interaction data to clinical impact

Despite significant research and clinical trials implemented to discover new drugs in the cardiovascular and other medical settings over the past decade, the approval of new treatments remains relatively low. This can be in part explained by a limited understanding of the multiple systematic impacts, including serious adverse effects, that candidate compounds have on a myriad of biological interaction networks underpinning disease phenotypes.

Knowledge about the interactions between drugs, their intended targets and the multiple seemingly unrelated biological processes that they can affect is essential to enable the development of new clinical applications. These interactions have been traditionally investigated in a reductionist fashion, which relies on the notion of identifying ‘single drug-single target’ associations. The characterization of such relationships, their mechanisms of action and phenotypic effects have typically depended on in vitro assays and information about the chemical structure of drugs and their intended targets. Under such assumptions and simplifications of biological complexity, a drug binds a single molecular entity. This event in turn represents the triggering activation point of a linear ‘molecular pathway’, whose ‘downstream’ execution results in the desired phenotypic or regulatory effect (Figure 1A).

Notwithstanding the progress facilitated by such views of biological phenomena, the exhaustion of the ‘single drug-single target’ discovery paradigm for novel drug discovery is becoming evident. This is reflected in large part in the paucity of new approved drugs and their massive development costs. In comparison with other medical domains, such as oncology and psychiatric disorders, cardiovascular research is lagging behind. Therefore, a comprehensive understanding of the interactions of drugs and biological systems opens new possibilities for translating fundamental ‘omic’ research into clinically relevant applications. This means, for instance, cost-effective approaches to predicting serious adverse effects of drugs in early development or post-marketing stages, as well as the discovery of new clinical indications of approved drugs.

The analysis of networks of interacting gene products and therapeutic agents represents a logical and more accurate extension of our understanding of disease, treatments, and their responses. This has been made possible by the accumulation of diverse pre- and post-genome era information at increasing rates, as well as by advances in computational analysis and modelling at different biological resolutions. At the centre of such systems-level approaches is the integrated representation of drug–drug, drug–target, and protein–protein interactions as complex maps of nodes (or vertices) interconnected via edges (or links) (Figure 1B). Thus, nodes can represent drugs or gene products, whereas edges can specify either physical interactions or other biologically relevant associations. Networks are computationally inferred, visualized, and dissected using multiples data resources, including molecular readouts and drug label information stored in several databases. These interaction networks can in turn be derived or analysed in a disease- or tissue-specific context.

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The analysis of drug–target interaction networks significantly augments our knowledge of the mechanisms of actions of drugs and their adverse effects in patients. Similarly, their computational analysis is enabling new applications to match patients to optimal treatments, and to find new clinical indications of approved drugs. Although the route that goes from data generation to clinical applications is not straightforward, essential research factors and steps can be synthesized to approximate such a translational road (Figure 2). Multiple and diverse information resources provide the basis for the generation of interaction networks, which can be investigated through the application of computational techniques. These integrated, systematic analyses, and the resulting prediction models enable the discovery of new knowledge about the mechanisms and impact of therapeutic agents. This knowledge offers opportunities to be translated into clinical benefits in the form of new compounds, treatment optimization, and computing tools to assist medical decision-making.

Key concepts to assist interpretation, analysis strategies, and application examples will be discussed in more detail below. This review will conclude with a discussion of pressing challenges and future perspectives relating to our aspiration to achieve a predictive and personalized cardiovascular medicine.

2. Generation of drug–target interaction networks

Drug–target interaction networks are based on the aggregation of multiple types of pharmacological and clinically relevant associations (Figure 3). Typically, they comprise pair-wise relationships between drugs, targets, other gene products, adverse events, and phenotypes. Drug–drug interactions can be obtained from known interactions tested in vivo or in vitro. These interactions may also be established if the drugs are shown to induce similar molecular profiles, e.g. gene expression patterns in cultured cells, or if the drugs have been reported to have similar side effects. Drug–target interactions may refer to experimentally validated, physical interactions, or to an association established when the molecular activity of the target can be quantitatively correlated with the drug treatment. Protein–protein interactions represent another important category of network...
Figure 2 The road from drug–target interaction data to clinical applications.

Figure 3 Building drug–target interaction networks. Examples of key types of interactions: their meaning, sources and visualization.
components. This can include interactions between known drug targets and other proteins, or between proteins known to indirectly interact with targets. As in the case of drug–target interactions, these relationships may be derived from experimentally validated identifications or from computational predictions.

Interaction networks can also explicitly describe associations between drugs and specific adverse drug events (ADEs). As shown below, the specification of these connections can represent a key data processing step leading up to the inference of drug–target or drug–drug interactions. Networks edges can also incorporate, depending on data availability or research objectives, more detailed information that describes the type or characteristics of the interactions. This includes, for example, information about the control mechanism of the drug–target interaction (e.g. activation, inhibition), binding strength, protein-interacting domains, the source of interaction evidence, and indication of its predictive confidence level.

Interactions and their associated information can be retrieved from different types of public and proprietary resources. Textual information included in scientific papers and drug label inserts represent important resources to mine drug–drug and drug–ADE associations. This is commonly accomplished by applying different machine learning algorithms, including those that take advantage of advances in natural language processing, to large collections of carefully annotated records. Interaction identification can be significantly enriched by the analysis of electronic health records and specialized databases, such as DrugBank. Annotated drug–target interactions are also available in various databases, such as PharmGKB, SuperTarget, and STITCH, which can offer additional information and visualization options. Diverse protein–protein interaction databases, e.g. IntAct and MINT, can expand the depth or coverage of drug–target interaction networks.

### Table I: Key information resources for the generation and analysis of drug–target interaction networks

<table>
<thead>
<tr>
<th>Resource</th>
<th>Description</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>cmap</td>
<td>Associations between drugs, genes and diseases</td>
<td><a href="http://www.broadinstitute.org/cmap">www.broadinstitute.org/cmap</a></td>
</tr>
<tr>
<td>DrugBank</td>
<td>Pharmacological information about drugs and their interactions</td>
<td><a href="http://www.drugbank.ca">www.drugbank.ca</a></td>
</tr>
<tr>
<td>MANTRA</td>
<td>Drug–drug interactions derived from computational analysis of gene expression</td>
<td>Mantra.tigem.it</td>
</tr>
<tr>
<td>PharmGKB</td>
<td>Impact of genomic variation on drug response, drug–target interaction information</td>
<td><a href="http://www.pharmgkb.org">www.pharmgkb.org</a></td>
</tr>
<tr>
<td>SIDER</td>
<td>Drug–ADE associations inferred from patient data</td>
<td>sideeffects.embl.de</td>
</tr>
<tr>
<td>STITCH</td>
<td>Drug–target interaction database</td>
<td>stitch.embl.de</td>
</tr>
<tr>
<td>STRING</td>
<td>Known and computationally predicted protein interactions</td>
<td>string-db.org</td>
</tr>
<tr>
<td>SuperTarget</td>
<td>Drug–target interaction database</td>
<td>insilico.charite.de/supertarget</td>
</tr>
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Computational approaches can also be applied to predict new interactions based on chemical and genomic information, as further discussed below. This commonly involves matching known drug–target interactions via different predictive features, e.g. structure similarity or information about shared interactions. The resulting ‘training’ data sets and prediction models can detect new interactions for subsequent experimental validation. In addition, online data sets and algorithms are available to estimate associations between drugs and genes based on molecular similarity profiles. In this case drugs and genes are linked if the former induce molecular responses similar (or opposite) to those displayed by the latter under different physiological or disease conditions. A representative example of resources in this category is the Connectivity Map (cmap), which allows the interrogation of a collection of drug response data sets with user-defined queries.

The Gene Expression Omnibus (GEO) is becoming another valuable source to assist large-scale data mining of drug–phenotype, drug–drug, and other clinically important associations. Table I lists these and other key resources to support the generation and analysis of drug–target interaction networks.

### 3. Extracting knowledge from drug–target interaction networks

Once interaction networks are assembled, researchers can implement several standard and application-specific analyses including visualization, network topology analysis and their combination with other types of functional information. Moreover, researchers can predict novel interactions using prediction models built on reference (or training) data sets consisting of annotated interaction networks. Fundamental graph theory concepts, which have been widely applied in the context of protein–protein or protein–DNA interaction networks, have also shown to be useful for linking drug–target interaction networks to clinically meaningful insights (Figure 4).

The number of interactions displayed by a network node defines its degree. High degree nodes are commonly referred to as ‘hubs’. The identification of hub drugs (Figure 4A) may aid the characterization of side or off-target effects, and to elucidate seemingly unrelated biological relationships in different disease domains. Similarly, hub targets (Figure 4B) may represent promiscuous targets influencing multiple molecular pathways. Such nodes may also assist the detection of relationships useful to find new uses of drugs across clinical domains or to estimate unknown ADEs (Section 4). Measures of network ‘centrality’ are also useful to characterize the potential pharmacological roles of drugs and their targets. These measures basically allow researchers to pinpoint bottleneck or ‘bridge’ nodes linking highly connected, functionally specialized subnetworks. Such nodes may represent potential therapeutic targets because of their capacity to disrupt or activate information flows connecting different biological processes and cellular locations (Figure 4C).

In comparison with hub targets, the perturbation of putative bottleneck targets is in theory less likely to significantly alter the internal dynamics of specific biological processes. Thus, bottleneck targets may also represent suitable interventional strategies with relatively reduced adverse effects. Bottlenecks tend to represent nodes in the shortest pathway connecting any two nodes in the network. Measures of the separation of drug targets and known disease-driving genes in these networks can be useful to estimate biologically meaningful constraints, such as the number of molecular steps separating the nodes,
to achieve a desired treatment effect. Bottleneck nodes and their potential impact are a direct consequence of another interesting property observed in complex networks: modularity.

Network modules are groups of highly inter-connected nodes that can be significantly implicated in specific biological processes, cellular locations, or disease-driving pathways (Figure 4D). Modules can be automatically detected by applying network clustering algorithms. Their characterization is facilitated by online databases that link gene and drugs to biological functions or phenotypes. Through ‘guilt-by-association’ statistical analysis, candidate modules in drug–target interaction networks have proved to be useful to establish novel associations between drugs, disease, and potential clinical impact (Section 4). When the network analysis is driven by gene expression information, network modules, and their inter-module interactions may uncover similarities between different drugs on the basis of their modes of action. Also the incorporation of genetic information into network analysis can help to recognize the effect of gene variants on drug action, such as those influencing metabolism or...
signalling events. Moreover, the analysis of network connectivity may suggest novel combinations of targets or drugs that may result in more specific, effective, and safer therapeutic interventions.18

Networks of known interacting drugs and targets can be extended through the analysis of other data types, including independent molecular and pharmacological data that are not used to generate the networks. For instance, Keiser et al.20 assessed the level of structural similarity between drugs and their known targets. After estimating the predictive power of this information, they determined novel associations for unreported drug–target interacting pairs. Several of these interactions were experimentally confirmed, including an investigation of their physiological impact in mice.

The level of detail and coverage of known interaction networks can also be improved by considering genomic and pharmacological data in an integrated fashion.21 Yamanishi et al.22,23 developed methods that take advantage of available chemical structure information together with textual descriptions of the pharmacological effect of drugs. Based on this information drug–drug similarity scores were calculated. This was followed by the computation of protein sequence similarity scores between all pairs of proteins included in the network. With these drug- and target-specific information features, Yamanishi et al. built a computational model that can accurately predict known interactions. The model is based on the calculation of drug–target similarity scores, which in turn are based on the combination of drug–drug and target–protein similarity scores. The resulting prediction model can be applied to predict new drug–target interactions.

Another approach comprises the exploitation of the predictive power of network modularity in combination with different gene and drug-related information. For instance, Zhao and Li24 identified modules of closely related genes in terms of their associations with known drug targets. An algorithm further identified groups of drugs and diseases significantly associated with each gene module, which resulted in the definition of ‘co-modules’ of interrelated genes, drugs, and diseases. This type of analyses can guide the elucidation of novel targets shared by different drugs across clinical domains, as well as the study of comorbidities.

A more detailed discussion of clinical applications of drug–target interaction networks follows.

4. Translating network-derived knowledge into benefits to patients

Advances in the analysis of drug–target interaction networks will, in the long term, be manifested in new drugs and more effective strategies for patient treatment management. The elucidation of complex and novel functional network connections, including ‘off-target’ interactions, is already enabling two crucial clinically motivated applications: the prediction of ADEs and the repositioning (repurposing) of approved drugs.25,26

4.1 Adverse drug events

A significant segment of the patient population is given at least one prescription.27 This is likely to increase as new therapeutic advances are continually being introduced for the benefit of ageing societies. This, together with our limited understanding of the action mechanisms and interactions of old and emerging drugs, make the investigation of ADEs a critical public health need. Different approaches that combine a diversity of data resources and computational techniques are being implemented to address this challenge, including the prediction of serious undesirable drug–drug interactions.27 This is possible through the inference and analysis of networks of drug–drug, drug–ADE, and drug–target associations based on the data resources introduced above.28 A key advantage of these approaches is that ADE alerts do not depend on the analysis of self-reporting data of drug events. Moreover, such integrative network-based strategies can be implemented at relatively early stages of drug development or post-marketing.

Ball and Botsis29 assembled a large network of vaccine–ADE associations that allowed the specification of novel, non-obvious clinical associations, and complications. The analysis of this network, which consisted of thousands of nodes and millions of edges, highlighted the existence of several hub vaccines linked to significant ADE patterns. Among their findings, they showed associations between the HPV4 (human papillomavirus) vaccine and seizures, and between the rotavirus vaccine and serious gastrointestinal complications.

In another study, Cami et al.30 built a comprehensive network of drug–ADE associations across medical domains. Pair-wise drug–ADE associations were first extracted from the combined statistical analysis of drug safety, taxonomic, and biological data profiles. ADEs were obtained from a proprietary database that included all reported events for approved drugs as of December 2005. Using this information, Cami et al. created a mathematical model capable to assign drugs to ADEs in the network. The model was applied to predict ‘missing’ associations between drug–ADE pairs, which were not originally represented in the network. The predictive capability of the model was prospectively assessed with associations reported between 2006 and 2010. This analysis correctly detected the connection between several drugs approved after 2005 and ADEs, including the association of the anti-diabetic drug rosiglitazone with heart attacks.

These investigations are also resulting in more comprehensive, publicly accessible resources for supporting research (Table 1). These databases are the product of significant data annotation and integration efforts, and offer user-friendly tools for visualizing and mining ADE associations. One representative example is SIDER,31 which stores relationships between thousands of drugs and side effects. For some of these drugs, SIDER also offers information about the observed frequency of their side effects in patients.

4.2 Drug repositioning

Networks of interacting drugs and targets, alongside their associated clinical events, also lay the foundations for the discovery of new indications for approved drugs, i.e. drug repositioning. Several examples of the scientific novelty, cost-effectiveness, and potential clinical impact of data-driven, network-based drug repositioning have been reported in different medical domains.32–35 In comparison with other domains, such as cancer research, the area of cardiovascular diseases is falling behind with regard to the number of repositioning investigations. This includes the repurposing of non-cardiovascular drugs to treat specific cardiac conditions.

The integrated analysis of drug–drug, disease–disease, and drug–target associations has enabled the discovery of novel indications for approved drugs. Gottlieb et al.36 reported one such approach, in which drug–drug associations were estimated with chemical similarity and information about their common side effects. Relationships between targets were detected by combining information about their sequence similarity, their known physical interactions and ontology-based terms describing their biological functions. Disease–disease
associations were established by computing their similarity based on phenotype annotations as well as by automatically analysing research articles. Following further transformation and integration of such similarity profiles, Gottlieb et al. built a mathematical model that distinguished between true and false drug–disease associations. The model was then applied to predict new drug–disease associations for approved drugs. They assessed the validity of such predictions by comparing them with new drug indications ongoing clinical trials. Among the reported findings, progesterone was predicted as a new treatment for renal cell cancer.

In a related approach by Cheng et al., drug–target, drug–drug, and target–disease interaction networks were generated by combining different data resources, such as those storing known drug–target interactions and structural similarity between drugs. Their method assigns a ranked list of candidate drugs for repositioning to every target in the network. A central contribution of their investigation was a computer program that determines novel drug–target interactions through the analysis of the multiple edges connecting drugs and targets in the network. In vitro experiments of some of these predictions showed that the cholesterol-reducing drug simvastatin can reduce the proliferation of breast cancer cells.

Network-driven approaches complement alternative repositioning approaches, such as those that comprise the large-scale analysis of drug–disease relationships based on molecular signatures. This category taps into significant amounts of public data generated by independent investigations in different areas. For instance, Dudley et al. predicted topirame (an anticonvulsant) as a potential new treatment for inflammatory bowel disease. This drug–disease association was established after matching publicly available gene expression profiles of drug responses with a gene expression signature of the disease.

Network-based approaches to drug repositioning will increase their applicability and impact as additional public resources specialized in supporting this task become available. The PROMISCUOUS data-base exemplifies ongoing efforts in this direction. It incorporates a comprehensive collection of approved, withdrawn, and experimental drugs (>25,000), as well as thousands of annotated drug–protein and protein–protein interactions extracted from multiple databases. This system allows users to input queries in different ways, such as drug names, and to interactively explore networks of interacting drugs and targets with known side-effects.

### 4.3 Applications in the cardiovascular research and clinical domains

Interaction network analysis approaches are augmenting our understanding of the cardiac effects of non-cardiovascular drugs, the impact of multiple drug combinations and ADEs. This has implications in the management of therapies routinely indicated in the clinical setting. A key application example is the assessment of potential drug interactions with the anticoagulant clopidogrel. Clinicians will be in a better position to address their concerns about possible detrimental effects through systems-level visualizations of known and putative interactions, together with tools capable to make recommendations on drug combinations or alternative treatments.

Significant evidence of the utility of network approaches to predict cardiovascular ADEs was reported by Keiser et al., whose method was introduced above. After identifying novel off-targets for different approved and investigational drugs, they found that motilium, a drug used to alleviate nausea and vomiting, could lead to adverse cardiovascular effects. Indeed this drug had been hitherto withdrawn after the US Food and Drug Administration (FDA) reported serious complications, such as cardiac arrest. Keiser et al. independently determined this association by identifying adrenergic blockers as new targets for motilium, which may partly explain the observed ADEs.

Tatonetti et al. recently reported an example of the prediction of unknown cardiovascular ADEs. Their computational prediction model first learned to detect true ADEs based on information extracted from millions of known event reports. In addition, they uncovered associations between ADEs with shared drug targets by mining interaction information in DrugBank among other databases, and performed prediction comparisons against the SIDER database. Another significant contribution of their investigation is the extension of the model to predict ADEs of co-prescriptions. For instance, they predicted that the combination of thiazides and selective serotonin re-uptake inhibitors (SSRIs) can potentially cause prolonged QT intervals. The likelihood of observing this effect is substantially reduced when patients are treated with either thiazides or SSRIs alone. Although further independent evaluations will be required and the molecular mechanisms behind this cardiovascular effect have not yet been outlined, Tatonetti et al.’s models represent a powerful and elegant approach with potential in different clinical domains.

A recent development specifically aimed at cardiovascular research is the Myocardial Infarction Drug-Target Interactome network (My-DTome) (Table 1). My-DTome was generated through the integration of multiple drug–drug, drug–target, and protein–protein interaction data sets relevant to the human myocardial infarction setting. It includes a comprehensive collection of approved drugs and investigational compounds, as well as their interactions with potentially novel targets (Figure 5A).

Computational analyses have shown that My-DTome is organized into highly interconnected regions of drugs and proteins, topologically, and biologically speaking. Such modules are significantly implicated in a diversity of biological processes, pathways and events of clinical interest. My-DTome thus provides a basis for novel network-driven approaches to investigating the cardiac impact of drugs, including those not approved in the cardiovascular disease setting. The application of My-DTome to assist the characterization of cardiovascular ADEs has been reported. Moreover, its predictive potential in drug repositioning is being investigated in combination with in vitro and in vivo animal models.

Illustrations of the application of My-DTome to explain potential cardiac effects of non-cardiovascular drugs are displayed in Figure 5. As a first example (Figure 5B), varenicline, a smoking cessation drug whose potential adverse cardiovascular effects have been investigated, was used to query My-DTome. Although varenicline is not explicitly represented in My-DTome, this drug is known to interact with CHRNA3 (cholinergic receptor, nicotinic, alpha 3), which is a member of a My-DTome module statistically associated with several biological processes (Module 14). More interestingly, such a module shares multiple interactions with other two modules (Modules 13 and 16) that are strongly implicated in several cardiovascular mechanisms and disease phenotypes (Figure 5B). Among them: calcium signalling, coagulation cascades, and dilated cardiomyopathy.

Figure 5C graphically summarizes potential mechanisms that can explain the adverse cardiovascular effects of rosiglitazone, an antidiabetic drug previously shown to be associated with heart attacks and mortality. Rosiglitazone is shown as a member of a highly
Figure 5 Application of drug–target interaction networks in cardiovascular research. (A) A graphical display of the My-DTome network, which encodes hundreds of drug–drug, drug–target and protein–protein interactions relevant to the treatment of myocardial infarction, including non-cardiovascular drugs. My-DTome can be mined to investigate the cardiac impact of non-cardiovascular drugs, as exemplified in (B) and (C). (B) The global view of significant molecular routes establishing the potential cardiovascular impact of varenicline, a smoking cessation drug. (C) Potential cardiac impact routes of rosiglitazone, an antidiabetic drug. Modules refer to highly-connected groups of gene products (and drugs) statistically associated with cardiovascular processes or events. Partial views of interactions are shown to facilitate interpretation.
interconnected, functionally compact community of drugs and proteins in My-DTome (Module 13).54 Instances of known drug–drug and drug–target interactions are depicted (Figure 5C). As illustrated in the previous example, Module 13 was statistically associated with important cardiovascular-related processes. Moreover, it shares multiple drug–drug, drug–target, and protein–protein interactions with other My-DTome modules: 4, 16, and 23, whose perturbations may directly impact several clinically meaningful, heart-related molecular states.

Huang et al.50 built a computational model that predicts cardiotoxicity of drugs based on the integration of gene functional annotations, drug–target interactions, and protein–protein interaction data. The model was trained on a data set in which each drug is described on the basis of their known associations with ADEs and the drug’s interactions with different targets. Their model could automatically establish connections between hundreds of drugs and 29 cardiovascular ADEs, including myocarditis, tachycardia, and heart failure. Their investigation also allowed the identification of novel ‘off-target’ proteins potentially implicated in cardiovascular ADEs, such as mediators of epinephrine and neurotransmitter norepinephrine.

More recently, Liu et al.51 reported a related approach that was capable to detect ADEs linked to cerivastatin (Baycol), a withdrawn cholesterol-lowering medication. Moreover, the model predicted cardiovascular complications associated with another withdrawn drug: the anti-inflammatory rofecoxib (Vioxx). As in Huang’s model, this approach exploits public information about drugs and their known targets and similar ADEs. However, a distinguishing aspect of Liu et al.’s approach is that each drug is also described by hundreds of chemical and biological properties. The model was built and tested on 832 FDA-approved drugs and 1385 ADEs, including non-cardiovascular complications. It accurately specified associations between cerivastatin and rhabdomyolysis, myopathy, myositis, myalgia, and muscle cramps. The model also predicted associations between rofecoxib, chest pains, and myocardial infarction. Such associations would not have been detected by only establishing chemical structure similarities between these drugs and other compounds with analogous ADEs.

Cardiovascular adverse events have been mainly identified by mining databases of molecular interactions, drugs, and post-marketing event reports. When patient records have been analysed, this has typically been based on clinical surveillance reports or patient records covering multiple disease domains. Key examples of cardiovascular ADEs that have been predicted by analysing different molecular or clinical data resources include: myocardial infarction, chest pain, and atrial fibrillation. On one level, this further highlights the potential of drug–target interaction network approaches to predicting specific cardiovascular ADEs. On another level, this underlines the need to further exploit patient-specific information stored in clinical databases in the cardiovascular setting.

With the emergence of new prediction models, such as those already successfully applied to detect ADEs, there is a necessity to complement them with techniques that can explain or delineate the mechanisms underpinning the resulting predictions. For example, a key question is: through which molecular routes or processes specific drug–drug interactions or ADEs occur? Within the cardiovascular research context, My-DTome represents a starting point to address this type of questions. Other major unanswered questions are: how the perturbation of specific interaction networks is manifested across multiple biological levels: from cellular through organ to the individual levels? How predicted drug–target interactions or ADEs directly modify quantitative risk of future cardiovascular complications or death? How network-based models can be dynamically integrated into the design and implementation of clinical trials? Success in these areas will also depend on the development of improved, community-driven approaches to classify drugs and their reactions in both human- and computer-readable formats.58

These questions and novel applications will also require further integration with human genotype information to aid the estimation of drug efficacy and safety, as well as to improve clinical outcomes. To offer new treatments or clinical event prediction models tailored to personal needs, finer-grained models that account for age, sex, comorbidities, and family history will be necessary. Breakout progress will be possible only through closer cooperation between the
computing, life, and clinical sciences. In addition, the size and complexity of the resulting computing systems must motivate the continued involvement of statisticians and informaticians in all stages of research and development.

In summary, the analysis of drug–target interaction networks and related information exemplify the translation of many years of fundamental, multi-disciplinary research into novel clinical applications. In the long run, this will be reflected on better treatments of cardiovascular disease, as well as advanced tools to personalize health care. In the near future, this area is likely to continue enabling progress in two key areas: the early prediction of adverse drug effects, and the discovery of novel uses of existing drugs, including those not approved for the cardiovascular disease setting.

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References


