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THEMED ISSUE REVIEW

Network medicine and systems pharmacology approaches to predicting adverse drug effects

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Identifying and understanding the relationships between drug intake and adverse effects that can occur due to inadvertent molecular interactions between drugs and targets is a difficult task, especially considering the numerous variables that can influence the onset of such events. The ability to predict these side effects in advance would help physicians develop strategies to avoid or counteract them. In this article, we review the main computational methods for predicting side effects caused by drug molecules, highlighting their performance, limitations and application cases. Furthermore, we provide an overall view of resources, such as databases and tools, useful for building side effect prediction analyses.

KEYWORDS
data mining, drug side-effects estimation, network medicine

1 | INTRODUCTION

Drug molecules are chemical compounds that, interacting with their protein targets, can induce beneficial and adverse changes in the human body, known as drug side effects. Evaluating the drug side effects is crucial for advancing drug safety assessment both in development of new drugs (de-novo drug discovery), but also in the repurposing of approved drugs for new diseases (drug repurposing), where there exists the possible occurrence of unexpected side effects in the context of the novel drug's use (Bouvy & De Bruin, 2015). Predicting drug side effects appears as a complex challenge due to the multifaceted relationships between drug compounds and various cellular components, and to additional factors like individual variability, genetic differences and the dynamic nature of biological pathways. Increasing effort has been then placed by the scientific community (Figure 1) on the development of computational tools that could forecast adverse reactions associated with drug compounds to gain insights into safer drug development and drug repurposing, balancing predictive accuracy with model interpretability (Sachdev & Gupta, 2020). This review aims to summarize and discuss the main computational strategies (and related tools) addressing this issue, which can be broadly classified into (i) molecular docking-based approaches, (ii) network-based approaches and (iii) machine learning (ML)-based approaches (Sachdev & Gupta, 2020). The rationale behind this classification is based on the key characteristics of each technique:- docking-based methods are considered those that rely on structural molecular data, network-based methods as those exploiting the interactions among drugs, targets and side effects to uncover unknown drug-side effect relations based on the closeness of different network entities, without

Abbreviations: AUC, area under the receiver operating characteristic curve; CPI, chemical-protein interactome; LQTS, long QT syndrome.

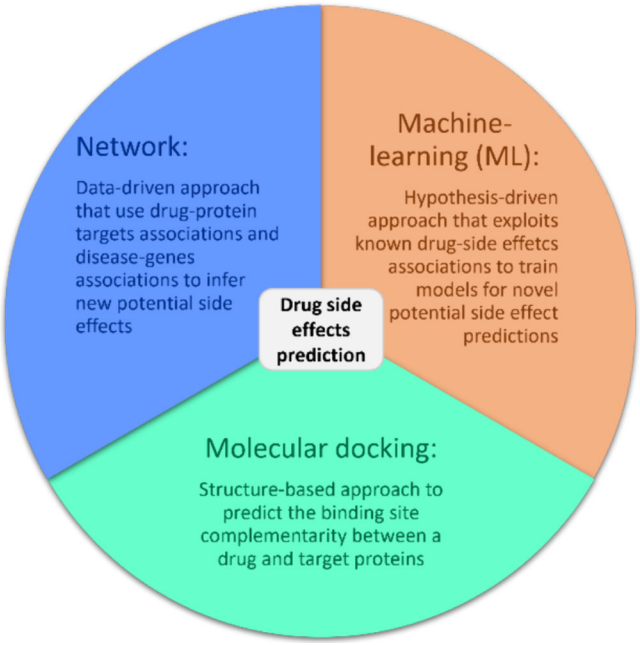

FIGURE 1 Main strategies that can be used for adverse effects prediction tasks. This classification is oriented towards the main themes, but this does not exclude those strategic approaches can marginally overlap. For example, machine learning methods can be used to predict associations based on networks or docking information.

a priori knowledge, and machine learning-based methods as those based on input–output models requiring a training phase (Figure 1).

Despite the variety of conditions involved in the onset of side effects, the common denominator is that they originate from the binding between drug molecules and target proteins. The approaches based on molecular docking involve a wide-ranging binding analysis evaluating the pool of possible interactions, focusing especially on off-target ones (LaBute et al., 2014). Network-based approaches aim to gain both a global and detailed understanding of the complex molecular interaction mechanisms that can lead to adverse outcomes. Exploiting tools and concept of the network medicine paradigm to show that the proximity of drug-targets and disease proteins in the human protein–protein interaction network (PPI or interactome) can predict both therapeutic effects and side effects (Paci et al., 2022). Machine learning algorithms offer a promising approach to address this complexity, owing to their ability to integrate large amounts of data, even of a different nature. These algorithms unveil the intricate relationships between drugs and side effects by leveraging heterogeneous data sets, automatically delineating the type of data that can be most informative in prediction. Analysing the research studies published up to 2024 (Figure 2), we observe an increasing trend of publications in this field (Figure 2a) and a shift from traditional docking methods to those based on machine learning in the last decade (Figure 2b). The growing adaptation of unsupervised machine learning algorithms is due to their ability to work with large datasets, whose

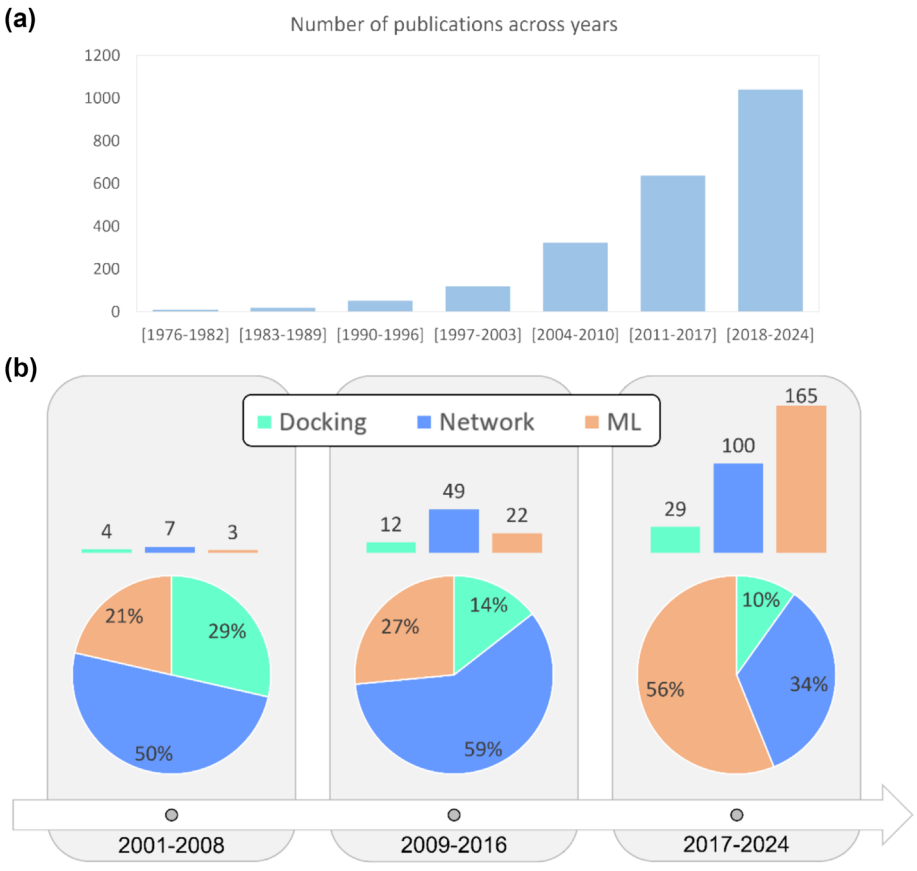

FIGURE 2 Number of publications related to a drug's side-effects prediction. (a) Barplot showing the number of research studies for each time interval considering PubMed-based research including the terms: 'identification', 'prediction', 'side effect' and 'adverse drug reaction'. (b) Number (top) and percentage (bottom) of research studies for each time interval regarding the three main discussed categories of methods presented in the legend (i.e. narrowing the PubMed search to docking-based, network-based and ML-based approaches).

size progressively increases over time (Dash et al., 2019) and whose contents would be difficult to handle without automated analysis approaches. Our aim is, thus, to provide and discuss a current snapshot of the advances of the computational methods in the drug-side effects prediction, describing the main algorithms in each category, together with the tools and related databases.

2 | DATABASES OF ADVERSE DRUG REACTIONS (ADRS)

Regardless of the type of approach used, known information on side effects represents an indispensable resource in building predictive models and evaluating them. The databases containing data on adverse drug reactions of which we are aware are listed in Table 1.

3 | DOCKING-BASED METHODS

An effective approach for evaluating the pool of possible off-target protein receptors of drug molecules, potentially linked to the onset of a side effect, is molecular docking. This uses the three-dimensional structural features of proteins and pharmaceutical molecules (LaBute et al., 2014). A common practice among pharmaceutical companies is the use of *in vitro* toxicity panels, dedicated to the analysis of interactions of a drug molecule with a limited pool of protein receptors delineated as decisive (Xu et al., 2018). Aiming to achieve broader coverage of protein targets, the use of molecular docking would allow for proteome-wide results, while minimizing analysis costs (Chen & Ung, 2001). There exist two main docking strategies:- traditional and reverse molecular docking. The traditional molecular docking follows the 'one target - many ligands' logic and identifies potential pharmaceutical molecules that bind to a specific target protein by calculating the binding affinity. This leads to the development of docking-based target prediction methods with a drug discovery-oriented approach. Docking engines (i.e. software designed to simulate the interaction between a protein and a molecule, called a ligand, to predict how they bind to each other) benefit from improvements in conformational sampling techniques, solvent modelling methods, computational efficiency and result interpretation strategies to enhance their accuracy and reliability in predicting protein–ligand interactions. The reverse molecular docking follows the 'one ligand - many targets' logic, reverting the roles of the actors in the classic analysis (Kharkar et al., 2014; Xu et al., 2018). This variant of traditional docking is most suitable to constructing a virtual screening panel of drug targets in which the binding between a pharmaceutical molecule and a large set of proteins is evaluated. Thus, by highlighting the link between a drug and proteins with known associations to side effects, reverse-docking enables the construction of docking-based adverse effect prediction methods. Compared with traditional docking, which focuses on the analysis of a limited number of ligands, reverse docking is more challenging because it screens a very large number of proteins. Furthermore, the results strongly depend on the completeness and quality of the target protein database. To explore these approaches further, in this section, we will first introduce reference databases that host structural information related to target proteins and pharmacological small molecules. Additionally, we will highlight the major web servers and software tools used for predicting interactions between small molecules and target proteins. Lastly, we will present some cases of application of docking-based techniques for predicting side effects.

3.1 | Web servers and databases

Considering the structure-driven nature of docking-based approaches, databases containing chemical-structural information of target proteins and drug molecules, particularly 3D architectures, are a key resource (Tatonetti et al., 2012). Most structural information comes from techniques for analysing (three-dimensional) biological structures such as X-ray crystallography (XRD), nuclear magnetic resonance (NMR) spectroscopy and cryo-electron microscopy (cryo-em).

Drug-target interactions are largely based on stable tertiary protein structures, either from X-ray crystal structures or mean-field NMR structures. Cryo-em has demonstrated that there is an ensemble of conformations for most proteins. Thus, the drug-target interactions (that lead to beneficial or adverse drug effects) that are not predictable based on these typical approaches (that is, the easiest conformation to crystallize) may be a consequence of the drug interacting with a different conformation. A compendium of each protein structural ensemble of states from cryo-em could offer yet another strategy for further refining drug-target interactions that cause adverse effects. Moreover, although data are limited, when exploring beneficial or adverse drug effects, it should be taken into account the allostery mechanism, in which the structure and activity of a protein are modified by the binding of a metabolic molecule at a site other than the chemically active one (Zhang & Nussinov, 2019).

Some of the most influential databases currently available are presented in Table 2.

Given the high level of expertise required to perform docking analyses, especially on a large scale, multiple web servers and dedicated software have been developed to make this approach faster and more accessible. The structure of the different tools follows a recurring pattern, consisting of a docking engine followed by a scoring function. The docking engine is a program that performs a structural analysis of the ligand and protein to determine the optimal position and orientation of a ligand within a protein binding site. These programs are commonly classified into three categories (Pinzi & Rastelli, 2019):- (i), systematic search algorithms, (ii), stochastic algorithms and (iii), deterministic search algorithms. After the identification of binding conformations, the interaction between ligand and protein is evaluated and ranked using a scoring function. Scoring functions are also divided into three main categories (Pinzi & Rastelli, 2019):- (i), force field-based, (ii), empirical and (iii), knowledge-based. Some of the web servers and software that can be used in the task of predicting side effects by performing molecular docking techniques are presented in Table 2. Please note that some of these servers are no longer accessible online (SEPreSA, Yang et al., 2009 and DRAR-CPI, Luo et al., 2011) but can still be a source of inspiration in designing predictive analyses.

TABLE 1 Databases containing information on side effects ('Year' refers to the latest update).

Database	Description	Year-ref.
SIDER (Side Effect Resource)	- Contains 139,756 known associations between 1430 drugs and 5868 side effects, 39.9% of which have information on frequency	2015-(Kuhn et al., 2016)
FAERS (FDA Adverse Events Reporting System)	- Includes details regarding 28,150,675 adverse events in humans, which have been reported to the FDA by pharmaceutical companies, healthcare professionals and consumers	2024-(C. for D. E. and Research, 2023)
onSIDES (ON-label SIDE effectS resource)	- Comprises a total of 2.8 million side effects for less than 2000 drugs, extracted from the FDA's Structured Product Labels (SPLs)	2023-(Tatonetti, n. d.)
offSIDES (OFF-label SIDE-effectS resource)	- Includes information about drug side effects that are not listed on the official FDA label	2019-(Tatonetti et al., 2012)
twoSIDES (drug-drug interaction SIDE-effectS resource)	- Covers millions of potential adverse side effects related to 63,000 combinations (pairs) of more than 3300 drugs	2019-(Tatonetti et al., 2012)
KidSIDES (pediatric SIDE-effectS resource)	- Contains risk information across paediatric development stages for 460,837 side effects	2022-(Giangreco & Tatonetti, 2022)
AwareDX (Analysing Women At Risk for Experiencing Drug toXicity)	- Contains 20,817 side effects with their sex-specific risks	2020-(Chandak & Tatonetti, 2020)

3.2 | Application cases

The wide-range search for protein targets of pharmacological small molecules, linked to the development of side effects or potentially toxic effects, represents a fundamental step aimed at avoiding risks to public health and huge economic losses (LaBute et al., 2014).

To address the issue, Ung et al. developed the INVDOCK inverse docking procedure (Chen & Ung, 2001). The goal of this method is to delineate the drug-side effect associations that also involve off-target proteins. The authors selected a pool of 1040 Protein Data Bank (PDB) entries, corresponding to 38 types of proteins, whose association with toxicity and side effects is based on information from biochemistry literature. A built-in biomolecular cavity database ('pocketome') was constructed from these entries. In addition, the 3D structures of 11 small molecules derived from the ACD3D database of MDL's or Woodcock's molecular models (Chen & Ung, 2001) database were considered. INVDOCK performs a prioritized automatic search across the entire protein database to identify target proteins for a given small molecule. Each docked structure is evaluated in terms of a scoring function, based on the energy function of the ligand-protein interaction, and compared with other ligands to statistically define a threshold for screening plausible bindings. A structure with a score below the threshold is considered successfully docked. Considering the previously introduced data, this algorithm successfully identified 89% of protein drug targets in the absence of drug-target covalent bonding. This method, by identifying possible drug-target interactions, allows us to infer the correlation between drug and side effect mediated by the protein targets. It is worth noting that the notion of the 'pocketome' (i.e. encyclopaedia of about 1000 experimentally solved conformational ensembles of druggable binding sites in proteins) as a first-pass strategy for docking interactions, while often useful, neglects that very real possibility that a small molecule can induce a binding pocket. The use-dependent inhibition of ion channels by several antiarrhythmic drugs could serve as an example of this phenomenon (Pugsley et al., 2001).

The need for extensive docking calculations in these analyses requires significant computing resources. As a result, some docking algorithms have been optimized for high-performance computing machines. In this context, LaBute et al. conducted an in-silico screening of drug candidates for potential adverse drug reactions using the molecular docking program VinaLC (LaBute et al., 2014), which uses Message Passing Interface and multithreading for parallelization of algorithms. The authors selected a set of 85 adverse drug reactions from SIDER and a list of 560 adverse drug reaction-related drug structures, obtained from the 'Orange Book' of approved products (C. for D. E. and Research, 2024). Then, 409 experimental protein structures were acquired from PDB, considered as generic targets in the DrugBank database. With the use of the docking program, they inputted the PDB protein structures and the drug structures to generate a 560×409 'off-target score matrix' containing the drug-target association scores. Furthermore, to compare the quality of the prediction based on off-target interactions, the 'on-target matrix' was built. This 560×555 Boolean matrix outlined known associations between the drugs and a pool of 555 known protein targets. Sets of L1-regularized logistic regression models were trained on both the 'off-target' and 'on-target' Boolean matrices, aiming to predict the 85 side effects. The predictive performance of the off-target models, assessed in terms of area under the receiver operating characteristic curves (AUCs) during 10-fold cross-validation, is comparable with that obtained from the on-target models (0.60–0.69 and 0.61–0.74, respectively). AUC is a performance metric estimated from the receiver operating characteristic (ROC) curve. This curve is constructed on the sensitivity-specificity plane by calculating the values of sensitivity and specificity across different classification thresholds. By calculating the area enclosed by the ROC curve, the

TABLE 2 Databases, software, and web servers useful in molecular docking-based adverse drug reaction (ADR) prediction tasks ('Year' refers to the latest update).

	Name	Description	Year-ref.
Databases	PDB	- Contains the structures of over 66,907 human proteins determined by XRD, NMR or cryo-em.	2024-(Burley et al., 2017)
	sc-PDB (v.2017)	- PDB-derived, it comprises structural information on 16,034 ligandable binding sites from 4782 different proteins and 6,326 different ligands.	2017-(Chandak & Tatonetti, 2020)
	SM-TF	- Covers 934 3D structures of small molecule-transcription factor (TF) complexes from the PDB. SM-TF is based on 176 TFs from a variety of species.	2016-(Xu et al., 2018)
	DrugBank (v.5.1.11)	- Contains a comprehensive description of over 16,500 drugs, including FDA-approved, experimental, illicit, nutraceutical and withdrawn drugs. In addition to providing information on the drug indications and its related side effects, it provides 2D and 3D structures for small molecule drugs and biotech drugs, respectively.	2024-(Chen & Ung, 2001)
	Binding DB	- Provides information on 2,827,284 binding affinities between over 1,213,266 drug-like molecules and 9191 proteins.	2024-(Kharkar et al., 2014)
	ChEMBL	- Contains 2D structural information of almost 2.4 million bioactive molecules with drug-like properties. Additionally, it includes information about how small molecules interact with their protein targets, outlining their pharmacokinetic and pharmacodynamic characteristics.	2023-(Burley et al., 2017)
Web server/ software	DOCK (v.6)	- Performs the identification of potential binding geometries and interactions of a molecule to a target. - It includes both rigid body docking and flexible ligand docking. - It mainly uses systematic search algorithms (incremental construction) followed by a physics-based scoring function. - Multiple settings are available to perform the search, and it is available in multiple versions.	2023-(Allen et al., 2015)
	SePreSa	- Uses the DOCK algorithm to calculate the interaction score between the input pharmaceutical molecule and 91 proteins known to be associated with ADRs. - The score is then subjected to a 2DIZ transformation to identify the most probable drug target. - Also predicts populations susceptible to ADRs by providing information on polymorphisms that involve amino acid residues in the binding.	2009-(Yang et al., 2009)
	DRAR-CPI	- Contains a collection of 385 structural models of 353 human protein targets and 254 active forms of 166 small molecules, each with a comprehensive description. - Given a small molecule as input, it identifies the most probable targets by first calculating the score using DOCK and then applying the 2DIZ transformation. - Also identifies drug–drug associations between small molecules with coherent interaction profiles through a measure of connectivity. - ADRs can be estimated based on both the targets and the ADRs of 'similar' drugs.	2011-(Luo et al., 2011)
	MDOCK	- Performs the docking of a ligand against multiple protein structures/conformations (inverse docking) by using the ensemble docking algorithm (Huang & Zou, 2007). - The energy function used is the knowledge-based scoring function.	2015-(Yan & Zou, 2015)
	INVDOCK	- Allows the identification of targets of a small molecule (inverse-docking) using a flexible ligand-protein docking algorithm followed by molecular mechanics energy functions.	2001-(Chen & Ung, 2001)
	AutoDock Vina	- Executes the dentification of targets of a small molecule using a hybrid scoring function derived from knowledge-based and empirical methods based on the X-score function. - The most probable binding conformation is identified through a stochastic optimization algorithm, consisting of Iterated Local Search global optimizer in addition to the BFGS method for local optimization.	2023-(Trott & Olson, 2010)
	VinaMPI	- An open-source parallelization of AudockVina designed for the use with distributed computing architectures based on Message Passing Interface. - Allows high-throughput inverse docking thanks to better performance compared to its predecessor.	2013-(Ellingson et al., 2013)
	VinaLC	- A modified version of AutodockVina with a mixed parallel scheme that combines MPI and multithreading designed for its application on large supercomputers. - Allows for the execution of reverse docking analyses.	2018-(LaBute et al., 2014)

Abbreviations: 2DIZ, 2-directional Z-transformation; ADR, adverse drug reaction; NMR, nuclear magnetic resonance; PDB, Protein Data Bank; XRD, X-ray crystallography.

AUC is obtained, which provides a comprehensive evaluation of a models ability to differentiate between positive and negative instances. An AUC close to 1 indicates the optimal performance of the classification model, whereas an AUC close to 0.5 indicates that the model is performing a random classification. The importance of predicting off-target interactions is highlighted by the fact that of the 409 protein targets used in the 'off-target' models, only 87 (21%) correspond to known interactions. The method is limited by the reliance on available 3D protein structures for molecular docking, biases in adverse drug reaction phenotype data towards approved drugs and the need for better drug-target interaction estimates and comprehensive protein sets for accurate adverse drug reaction predictions.

Some side effects are difficult to detect during the approval phases due to their low incidence and appearance after the drug has been marketed. Often, subgroups of the population in which these side effects occur are characterized by polymorphisms within binding pockets, making them more susceptible to side effects. To address this risk, Yang et al. developed SePreSA a server for predicting populations at risk for specific adverse drug reactions. The server includes 91 target protein structures, acquired from the DART (Ji et al., 2023) and DITOP (Zhang et al., 2007) databases, associated with adverse drug reactions (target adverse drug reaction). The possible binding of molecules submitted to the server is outlined through the DOCK program, which calculates a score for each drug-target combination, thus defining the chemical-protein interactome (CPI) adjacency matrix. Based on this two-dimensional matrix, the server calculates a relative drug protein interaction score (i.e. 2-directional Z-transformation (2DIZ) of the score matrix) to prioritize the targets that may be affine with the input molecules. This chemical-protein interactome is composed of all the molecules evaluated on the server by the user; therefore, the more molecules the user submits, the more exhaustive the chemical-protein interactome matrix will be. The performance of the server in target identification was tested by choosing 76 of the proteins present on the server that showed embedded co-crystallized ligands and providing these 86 co-crystallized ligands as input. The developers indicate an AUC of 0.82 in recognizing ligand-target associations, considering all the drug-target pairs with a Z′-score lower than −0.5. Because even this method is based on 3D structures, it strongly depends on the quality of the considered structures. Furthermore, the number of proteins associated with side effects is rather limited, which could overlook possible associations. The generic output of this server, given an input molecule, corresponds to (i), a list of adverse drug reaction targets probably interacting with it, (ii) the binding patterns, (iii) the amino acid residues that interact with the molecule and (iv), the information on the polymorphisms of each interactive residue. Thanks to this information, the authors highlighted a polymorphism (refSNP ID rs2233385) of the human cytosolic **sialidase 2** (HsNEU2), frequent in the Asian population, that could explain the higher susceptibility of the Japanese population to developing an acute neuropsychiatric disorder during the treatment with **oseltamivir** (i.e. an antiviral drug used to treat influenza).

The influence of this polymorphism was further investigated by Li et al. (2007) in a study that combines computational analysis of molecular docking with the *in vitro* validation of the results. The study highlights how these adverse drug reactions could be determined by a strong similarity between a human protein, HsNEU2, and a viral protein, viral neuraminidase. The authors demonstrated, through manual inspection of docking analyses, that HsNEU2 both shares the same active site residues as the viral protein and has the correct binding pockets for oseltamivir carboxylate. Thus, the drug could bind to the human protein as well as the viral one, causing the adverse reactions. To delineate the characteristics of docking between HsNEU2 wild-type and HsNEU2 R41Q (i.e. a variant that presents the nonsynonymous SNP, refSNP ID rs2233385, causing the substitution of Arg41 with glutamine [Gln]) with oseltamivir carboxylate, the complex drug-protein structures were built using Insight II, which also provides an empirical scoring function. From this analysis, it emerged that HsNEU2 wild-type can bind to oseltamivir carboxylate, but the binding is weakened by the basic side chain of Arg41, which could have a repulsive effect on the basic C4 group of the drug. In contrast, HsNEU2 R41Q showed a higher affinity to the drug because Gln41 would be less repulsive than Arg41 and would thereby allow for the creation of a negatively charged pocket thanks to the nearby acidic residues Glu39 and Asp46. The results from docking were confirmed by an *in vitro* analysis, using sialidase assays with the 4MUNANA substrate (i.e. fluorogenic substrate commonly used to measure *in vitro* sialidase activity). Despite the encouraging experimental validation, the high consumption of the drug by the Japanese population could represent a bias, and the hypothesis could be confirmed only after large-scale genetic studies.

The same developers of SePreSA have also designed a server called DRAR-CPI (Luo et al., 2011), based on mining a chemical-protein interactome. This server contains a collection of 385 structural models of 353 human target proteins and 254 active forms of 166 small molecules, accompanied by their description, indication and associated side effects. The DOCK program was used to explore all possible protein pocket–ligand configurations, resulting in a 254x385 matrix of docking scores. When a new drug is provided as input, the server calculates its scores and updates the matrix with the new terms. Subsequently, all elements in this matrix are transformed using the 2-directional Z-transformation (2DIZ), resulting in a matrix of Z′-scores. Considering the Z′-scores associated with the input drug, a Z′-score lower than −1 (greater than 1) corresponds to a favourable (unfavourable) target, used as target signatures. Then, based on these signatures, for each drug in the library, a connectivity score is computed to quantify the positive or negative association between the input molecule and the drug. When a specific molecule is provided as input, the server returns information on all potential targets that may interact with it, along with a list of drugs that exhibit a similar (or opposite) interaction profile. These outputs serve as a dual tool for predicting side effects, leveraging information from both off-target interactions and the side effects of similar drugs. To assess the quality of drug–drug associations, the server was benchmarked against relations predicted using gene expression profiles (Lamb et al., 2006), matching 74% of the associations. Although this server allows for

the simultaneous analysis of potential beneficial or adverse effects related to a drug, the performance of the side effect prediction task is not discussed.

4 | NETWORK-BASED METHODS

The fundamental elements of networks are nodes and edges. In this section, depending on the network-based approaches used for predicting side effects, nodes can represent various entities (e.g. proteins, drugs, diseases and side effects) and edges can symbolize the type of relationship between them (e.g. physical interactions, metabolic reactions, correlation relationships and connections derived from analytical assumptions).

4.1 | Application cases

Mizutani et al. developed a statistical model (Mizutani et al., 2012) for the construction of a drug target–side effect correlation network, based on the analysis of sparse canonical correlations (SCCA). This approach allows the detection of both the drugs that could be linked with the side effect and the mechanisms underlying its development. By combining the information acquired from DrugBank and SIDER, a pool of 658 drugs for which both the target and associated side effects were available was selected. For each drug, two binary profiles were constructed:- one related to its target proteins (1368-dimensional) and one related to its known side effects (1339-dimensional). In these binary profiles, the overall size of the two binary profiles (where '1' indicates the presence of the association, and '0' indicates its absence) is due to the number of elements associated with at least one drug in the library. Running sparse canonical correlations, they identified canonical components that represent the most correlated sets of proteins and side effects based on the co-occurrence of drugs in their profiles. The method allows to identify new potential side effects of a drug based on the correlation between its target protein profile and known side effects. Providing as input the drug protein binding profiles, the model achieved an AUC of 0.8895 ± 0.0002 (5-fold cross-validation) in recognizing known side effects. The biological coherence of proteins belonging to the same related sets was tested by functional enrichment analysis, showing significant enrichment in proteins belonging to the same biological pathways, albeit with different molecular functions. Because the side effect prediction is based on drug-target data, the prediction is constrained by exhaustive target profiling.

Exploiting a diffusion-based network approach, Yu et al. developed a new method, called mtADENet (Yu et al., 2024), which integrates structural and interaction information (i.e. known or predicted drug targets) to identify drug-side effect associations. This method allows for the identification of potential side effects for fully characterized drugs as well as for novel compounds. This method relies on two processes of network-based inference:- (i) a diffusion process performed on a substructure-drug-target network to predict new targets for both drugs and novel compounds and (ii), a diffusion process performed on a target-drug-side effect network to predict potential side effects for drugs and novel compounds, with known or computationally identified targets (from the previous step). The diffusion method consists of iterative propagation of 'resources' through the heterogeneous network. Initially, the resources are assigned to the drug of interest, which are then distributed to nearby nodes based on their connectivity. The 'resource' diffusion is iteratively repeated for a specified number (k) of times. The final amount of resources accumulated in a node (e.g. a side effect node) represents the prediction score, indicating the likelihood that the drug of interest is associated with that entity. The model capabilities were tested by constructing a series of prediction models for 23 side effect categories. These models achieved AUC values ranging from 0.865 to 0.942 in 10-fold cross-validation. Yet, mtADENet cannot provide predictions for a new side effect without any associated drug. Additionally, the frequency and severity of adverse events are not considered.

Focusing on long QT syndrome (LQTS; i.e. channelopathy related to altered cell signalling that can lead to fatal arrhythmias), Berger et al. developed a classifier based on the LQTS neighbourhood in the interactome for predicting LQTS-associated drugs (Berger et al., 2010). The authors implemented a random walk-based distance algorithm, based on the 'mean first passage time' (MFPT), to calculate a module distance score. This score was used to measure the distance between 13 genes known to be associated with LQTS (LQTS module) and all other genes in the interactome. By considering only genes with a score greater than 1 (i.e. genes whose distance from the LQTS module is less than the average distance of the gene from any node in the network), the LQTS neighbourhood was identified. Using the 100 known drug-LQTS associations acquired by FDA adverse events reporting system, as a reference, the performance of the LQTS neighbourhood as a classifier was evaluated by AUC in three different settings:- (i), for the classification of drug targets, considering drug targets known to induce LQTS as true positives, (ii), for drug classification, associating each drug with its highest-score target and considering drugs known to induce LQTS as true positives and (iii), for classifying drug classes (i.e. drugs sharing the same highest-score target), considering drug classes that include drugs known to induce LQTS as true positives. The AUCs obtained are 0.67 (P value = 0.002), 0.71 (P value = 0.006) and 0.70 (P value = 0.001), respectively. This pipeline is adaptable for studying other drug-induced side effects. Considering the potential increasing size of the interactome network due to the new discovered interactions, calculating the mean first-passage time on large networks can become computationally very expensive.

The LQTS was further explored and used as a case study in the work of Paci et al., who presented a new approach to predict side effects associated with repurposable drug candidates (Paci et al., 2022). The authors analysed nine cardiovascular diseases and two side effects (LQTS and asthma), retrieving the genes associated with these conditions from Phenopedia and literature-based studies, and the targets of 1873 FDA-approved drugs from DrugBank. The

rationale of the study is that, just as drug targets close to a disease module could indicate a repurposable candidate, drug targets close to a side effect module could indicate their role as trigger (Paci et al., 2022). The distance between a drug and a module is measured using an adjusted similarity measure implemented by SAveRUNNER algorithm (Fiscon & Paci, 2021). A drug is considered proximal (distal) if its adjusted similarity is ≥0.5 (<0.5). Four modes of action have been defined to classify a drug, based on their being proximal/distal to a disease/side effect. A drug proximal to the disease and distal from the side effect is considered a safe repurposable candidate. Focusing on the results of the drug-side effect classification analysis, this approach achieved an accuracy greater than 70% (AUC = 0.72) in identifying drug-LQTS associations established by SIDER. By excluding LQTS-related drugs from the repositionable candidates against cardiovascular diseases, the classification task reached an accuracy of ∼70% (AUC = 0.70) in recognizing known drug-disease associations. A limitation of this approach based on network proximity on the human interactome network could be the lack of information about the directional change in gene expression profiles in treated human tissue or cell lines, which either attenuate or amplify the perturbation causing the side effect. In addition, the incompleteness of the current human interactome prevents all the interactome-based methods from reaching their full potential on drug-side effect predictions.

Kiouri et al. developed a network-based strategy to predict side effects of repurposed drugs and applied it on repurposed antihypertensive sartans (i.e. AT_1 antagonists e.g. **losartan**) for COVID-19 (Kiouri et al., 2023). They constructed a protein-drug network by (i), obtaining target proteins of the drug from DrugBank, (ii), identifying other drugs targeting these proteins from DrugBank, (iii), mapping these targets onto the human interactome (from PICKLE [Dimitrakopoulos et al., 2021]) and identifying first neighbour proteins, (iv), identifying secondary drugs targeting these first neighbour proteins and (v), merging this relational information to build the network. This network predicts potential off-target side effects by examining interactions with first neighbour proteins, which could act as off-targets, and by performing functional enrichment analysis (using BiNGO [Maere et al., 2005] or PANTHER [Mi et al., 2019; Thomas et al., 2022]) and disease association analysis (using DisGeNET [Piñero et al., 2019]). It also highlights potential drug–drug interactions. The authors applied this method to Pfizers **paxlovid**, an antiviral drug approved for emergency use in treating mild-to-moderate COVID-19. The gene-disease association showed that the protein targets of sartans are mainly involved in cancer, cardiac complications and pregnancy loss, and paxlovid targets are associated with obesity, liver diseases and diabetes. Sartans are primarily involved in protein and enzyme binding, and paxlovid-related proteins are mainly involved in transcription regulation, potentially leading to different side effects. The analysis found no critical issues from combining paxlovid and sartans. Although the study is based on experimental data, it cannot fully replicate the complexity of pharmacological interactions and potential side effects *in vivo*. Additionally, other factors that could influence the efficacy and safety of the drugs, such as patient characteristics and dosage, are not considered.

5 | MACHINE LEARNING (ML)-BASED METHODS

There are numerous machine learning algorithms that can be employed in classification tasks. They generally share a common structure, divided into training, validation and testing phases. During the training phase, the model learns from the analysis of data based on the experience, aiming to identify patterns connecting drugs to side effects. In the validation phase, which is crucial for the model to be generalized to new data, parameters are optimized to achieve an optimal classification. Finally, during the testing phase, the model's performance in classifying new data is evaluated. Machine learning methods covered in this review can be classified into (i), clustering methods, automatically grouping data based on similarities or shared characteristics, (ii), random forest methods: creating an ensemble of random decision trees for classification or regression, (iii), deep neural networks (DNNs), based artificial neural networks with multiple hidden layers, (iv), graph convolutional networks (GCNs) - extended convolutional neural networks which operate on graphs and (v), matrix decomposition-based methods, based on a factorization of a matrix into simpler components to reveal its hidden structures.

5.1 | Application cases

To overcome the multifactorial nature of the problem of predicting side effects, which is dependent on the multiple characteristics describing a drug and the multiple effects that these could determine, Dimitri and Liò developed a machine learning algorithm called DrugClust (Dimitri & Lió, 2017). This algorithm takes two matrices as input:- a matrix of drug profiles (e.g.- protein interaction profiles, profiles describing the chemical structure or profiles of desired information) and a matrix of side effect profiles (i.e.- matrix describing the drug-side effect associations). The DrugClust pipeline is divided into 3 main phases:- (i—training phase) clustering of drugs in the feature space (choosing an algorithm among K-Means, partitioning around medoid or K-Seeds), (ii—training phase) construction of a probability score matrix calculated with a Bayesian approach, in which each element corresponds to the probability that a given cluster (defined by the specific row) is representative of a specific side effect (defined by the specific column) and, (iii—testing phase) assignment of a new drug to one of the pre-established clusters, based on the similarity measure from the centroid/medoid, with consequent determination of the expected side effect scores relating to that cluster. The performance of the algorithm was evaluated using three benchmark datasets: Mizutani et al. (2012), Liu et al. (2012) and Zhang et al. (2015). The performances measured in terms of the best AUCs obtained in the benchmark datasets are 0.89, 0.90 and 0.91, respectively. This approach allows the determination of groups of similar drugs in the multidimensional space, but it does not provide an explicit explanation of the biological features more influencing the definition of each group, except through functional enrichment analysis performed downstream of clustering.

Wang et al. built a novel deep neural network model (Wang et al., 2019) to identify potential adverse drug reactions deriving from drugs. The deep neural network exploits three types of drug features:- (i), chemical features, acquired from PubChem (Kim et al., 2021), (ii), biological features, obtained from DrugBank and (iii), semantic features based on biomedical literature information, retrieved from MEDLINE (Medical Literature Analysis and Retrieval System Online). The semantic features were extracted using the Word2Vec embedding method (Mikolov et al., 2024), also introducing a description mapping function to identify features relating to new drugs. The deep neural network architecture, a multilayer perceptron, includes dropout layers between each dense layer to prevent overfitting during training. Drug-side effect profiles, derived from SIDER, are added into the features. The last layer of the deep neural network is made up of a number of nodes equal to the number of considered side effects, modelled in order to obtain an output probability value relating to the drug-adverse drug reaction association. The predictive performance of the model was evaluated by training the network using information on drugs, including the related adverse drug reactions, reported up to 2009 and comparing the results with data from 2012. The number of drugs considered corresponds to 746, up to 2009, plus another 232 new drugs in the 2012 dataset. The model achieved the highest AUC in the prediction task using two hidden layers (AUC of 0.844). The authors highlight how semantic features are the most informative, while chemical ones are the least informative. The reliability and the feasibility of this model are highly dependent on the amount of input data that are heterogeneous and not easily accessible, demanding the need for open-source databases.

Zitnik et al. implemented Decagon (Zitnik et al., 2018), a new approach to predict side effects resulting from treatment with drug combinations or polypharmacy. Decagon is a nonlinear multilayer graph convolutional network model that exploits a large multimodal graph to identify potential side effects between drug pairs. The multimodal network is built by combining the following interaction networks:- (i), protein–protein (PPI) network, aggregated from PPI networks built in previous studies (Chatr-aryamontri et al., 2015; Menche et al., 2015; Rolland et al., 2014; Szklarczyk et al., 2017), (ii), drug-protein network, where the edges correspond to physical interactions acquired from the STITCH (Kuhn et al., 2014) database and (iii), drug–drug network, where the edges correspond to the side effects resulting from the polypharmacological treatment, obtained from twoSIDES (Tatonetti et al., 2012). Overall, the network is composed of 645 drug nodes and 19,085 protein nodes, connected by 715,612 protein–protein edges, 4,651,131 drug–drug edges and 18,596 drug-protein edges. Furthermore, each node is associated with features that characterize it, such as the side effects associated with a drug. The model is divided into two components:- (i), an encoder, a graph convolutional network that produces embeddings for each node in the graph and (ii), a decoder, a tensor factorization model that calculates the probability of association between pairs of drugs and side effects based on these embeddings. Parameter optimization is achieved using a loss function based on cross-entropy loss, with the model trained using the Adam optimizer. For each side effect, the pairs of drugs associated with it were divided into training, validation and test sets in the following proportions: 80%, 10% and 10%, respectively. During the side effect prediction task, Decagon achieved an AUC of 0.872, demonstrating its highest performance for side effects with a strong molecular basis. This algorithm strongly relies on the twoSIDES database, which also contains non-clinically validated associations, potentially impacting the reliability of its polypharmacy side effect predictions.

Aiming to exploit useful information hidden in clinical notes (CNs), Wang et al. designed an ML method (Wang et al., 2015) to identify associations between drugs and adverse drug reactions based on electronic medical records (EMRs). To build the core dataset, they extracted 1898 known drug- adverse drug reaction associations from the Medi-Span adverse drug effects database (Consultato, 2024) (positive associations) and added 4336 random associations (negative associations). This dataset was split into training (70%) and test (30%) sets. For each pair, a feature vector was created, consisting of the following components:- (i), 9 features computed using the NCBO Annotator-based text processing pipeline (Jung et al., 2015; LePendu et al., 2012) applied to 9.5 million clinical notes acquired by STRIDE (Stanford Translational Research Integrated Database Environment; Lowe et al., 2009), (ii), 9 features extracted by analysing known drug-adverse drug reaction associations from Medi-Span and (iii), 12 features related to drug indications retrieved from both Medi-Span and Drugbank. Next, a random forest model was trained on the training set and tested on the test set, achieving an AUC of 0.94. Furthermore, to identify new potential drug- adverse drug reaction associations, the classifier was tested on a dataset composed of 2,362,950 pairs relating to 1602 drugs and 1475 disorders (i.e. drugs and disorders that appear at least once in the STRIDE clinical notes). By setting a threshold on the confidence of the classifier (posterior probability of 0.7), 41,248 putative associations were identified. To reduce the rate of potential false positives inherent in analysing such many pairs, a filtering process based on FDA adverse events reporting system case reports and MEDLINE biomedical literature was applied, resulting in 240 predicted associations. The 36% of these associations were supported in both the Medi-Span standard reference and in the study of Harpaz et al. (2014). Dependence on clinical notes, which may contain incomplete or imprecise information, could limit this automated search for side effects. Additionally, the use of more advanced natural language processing techniques would be essential to evaluate not only the prevalence but also the severity of potential side effects.

Zhang et al. presented a novel computational approach called 'feature-derived graph regularized matrix factorization' (FGRMF) (Zhang et al., 2018). This method combines both known drug–side effects relationships and biomedical characteristics of drugs to detect new drug-side effects associations. The dataset used for associations is based on the work of Liu et al. (2012), with additional associations acquired from SIDER, for a total of 141,857 associations (involving 1430 drugs and 6742 side effects). Various feature vectors were constructed for each drug (including chemical, pathway, treatment, enzyme, transporter and target feature vectors). For each feature type, a drug–drug graph was constructed based on the Jaccard

similarity between different drug vectors, from which the corresponding adjacency matrix was derived. The novelty of the feature-derived graph regularized matrix factorization method lies in the incorporation of biomedical information into the matrix factorization (MF) process of the drug side effect association matrix. The goal of matrix factorization is to find two low-rank matrices whose product approximates the original association matrix, allowing prediction of unknown associations. To introduce feature-derived information into the matrix factorization process, a graph-based regularization term was added to the objective function used by the optimization algorithm to estimate the two low-rank matrices. The model was validated through 5-fold cross-validation (5-CV) in two ways:- (i), using only known drug side effects (5-CVI) and (ii), using all pairs of drug side effects (5-CVII). Regardless of the type of features used, the model achieved an AUC greater than 0.94 for both 5-CVI and 5-CVII. In both cases, the highest area under the precision-recall curve was achieved by using all features simultaneously. Although the model demonstrates the importance of biological factors in predicting drug side effects, it does not provide a comprehensive interpretation of the underlying biological mechanisms, which is useful for assessing drug safety.

Galeano et al. proposed a non-negative matrix factorization matrix factorization model for predicting frequencies of drug side effects (Galeano et al., 2020). Their algorithm learns latent drug and side effect signatures from a drug-side effect matrix of frequency classes, which are both reproducible and biologically interpretable. It is one of few methods that address the problem of estimation of frequencies of side-effects and show advantages in terms of prediction and interpretability. However, it did not exploit multi-view data of drugs and side effects, so its prediction performance could be further improved. In 2022, the same authors built a geometric self-expressive model (GSEM) to learn a global optimization representation of drugs and side effects and identify the potential candidate side effects for the drug (Galeano & Paccanaro, 2022). It starts from a known drug-side effect association matrix, encoding the presence or absence of drug side effects, and it learns both drug similarity matrix (built on chemical structure, biological targets and pharmacological activity) and side effect similarity matrix (built on similarities in anatomical and/or physiological phenotypes). By linearly combining these two models (i.e. drug self-representation model and side effect self-representation model), it returns as output a predicted score for each drug-side effect pair.

To enhance the accuracy of adverse drug reaction frequency estimation, Wang et al. (2023) proposed another method based on neighbourhood-regularization factorization (NRFSE), which also integrated three drug attributes (i.e. drug target Gene Ontology annotations, chemical structure and side effect frequency), and two side effect attributes (i.e. frequencies across drugs and Medical Dictionary for Regulatory Activities), ensuring that the most similar drugs and side effects exhibit similar latent signatures. The model also leverages nearest neighbours to create neighbourhoods of drugs and side effects and refine embeddings of new drugs and new side effects. The model performance was evaluated both in terms of the identification of drug-side effect association and in term of frequency value prediction, showing better overall prediction accuracy and AUC than other methods, including Galeano's model, tested on the same dataset under different settings.

The promising approach based on neighbourhood regularization method was exploited also by Azuma and Mizuno (2023), which proposed a neighbourhood regularized bidirectional matrix factorization (NRBdMF) method to predict drug effects that also incorporate bidirectionality, to take into account both the side effects and therapeutic effects of a drug, assigning a positive label (+1) to known side effects and a negative label (−1) to known therapeutic effects. The method performance was evaluated both in term of AUC and area under the precision-recall curve, showing AUC higher than 0.8 in different settings.

The potential limitation of these approaches relies on the partial knowledge about drugs, proteins and diseases similarities required as input data, as well as the use of only one dataset for drug-side effects known association, which may be insufficient in terms of the amount of information. In addition, for some approaches like Galeano and Paccanaro (2022), there exists also a lack of standardized datasets that classify side effects based on the phase of clinical trials.

6 | DISCUSSION

This review aims to review current knowledge in the field of adverse drug reactions predictions. Our literature analysis led us to group the strategies used for this purpose into three main categories: (i) molecular docking-based methods, (ii) network-based methods and (iii) ML-based methods. These approaches manage the complexity that characterizes the onset of side effects in different ways.

Methods based on molecular docking address the problem at its core by elucidating the structure interaction mechanisms between drugs and their respective targets. They focus particularly on identifying off-target proteins that could lead to phenotypically unknown outcomes, ensuring high precision and accuracy and aiding to identify novel drug-target bindings. However, involving the iterative molecular simulation of each drug with target protein 3D-structures, docking studies demand a high computational effort, often reducing the feasibility of this approach. In addition, their applicability strictly depends on the 3D structure information of drugs and proteins for adverse drug reactions prediction.

Network-based techniques, operating at a higher level of abstraction, allow to delineate significant relationships among numerous variables. By extracting information from complex biological systems, independently from structure information or a priori knowledge about drug-side effect association, these techniques can enable both comprehensive analysis and detailed exploration of potential biological motifs underlying adverse drug reactions. However, most of them lie on protein–protein interaction network, whose incompleteness and intrinsic immutable nature together with the partial knowledge of the number of proteins associated with side-effect can affect the adverse drug reactions prediction. Integrating information about the protein networks with molecular data and cellular functions could also enhance the performance of adverse drug reactions prediction.

ML methods are crucial for analysing large datasets, even those containing different types of data. Given a dataset describing an adverse effect and a set of certain outcomes, these algorithms autonomously learn the relationships between variables and outcomes. Despite the high performance, their fundamental limit lies in their challenging interpretability, which makes the biological understanding of the information flows problematic. Moreover, models trained on specific datasets may not be generalized well to new, unseen data and thus can lead to inaccurate predictions in different settings.

A straightforward comparison of the various methods cannot be conducted because different approaches use different datasets in all the prediction processes, and no standard dataset is available. Therefore, the selection criteria could be based on the issues addressed, the overall efficiency of the technique and their advantages and limitations. The heterogeneous nature of the data used in different models, which may include genomic, proteomic, phenotypic, chemical and clinical information, complicates the establishment of a common benchmark. Yet, focusing on the primary problem of predicting drug-side effect associations offers a potential solution. The effort of the scientific community could be in the ampliation and integration of the current databases collecting known drug-side effect associations, such as SIDER and onSIDES, in order to compare model based on their ability to recognize these relationships.

Given the specific characteristics of each type of here-discussed approach, the combination of different strategies can be even an added value for a complete predictive analysis.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander et al., 2023).

AUTHOR CONTRIBUTIONS

A. Funari: Investigation (lead); methodology (equal); writing—original draft (lead). **G. Fiscon:** Investigation (supporting); methodology (equal); supervision (equal); visualization (lead); writing—original draft (supporting). **P. Paci:** Conceptualization (lead); funding acquisition (lead); project administration (lead); supervision (equal); writing—original draft (supporting).

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CONFLICT OF INTEREST STATEMENT

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