DRUG INTERACTION PREDICTION USING PASS AND PoSMNA DESCRIPTORS

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DRUG-DRUG INTERACTIONS

- Predicting potential DDIs is one of the important activities that a pharmaceutical company undertakes before the approval of any new drug.
- Two million adverse drug reactions are reported annually, of which 26% can be attributed to avoidable drug-drug interactions (DDIs).
- DDI predictions are primarily governed by elucidation of the metabolism of any new entity.
- 73% of the top 200 drugs are cleared primarily by metabolism, of which 75% of the metabolism occurs due to cytochrome P450 enzymes.

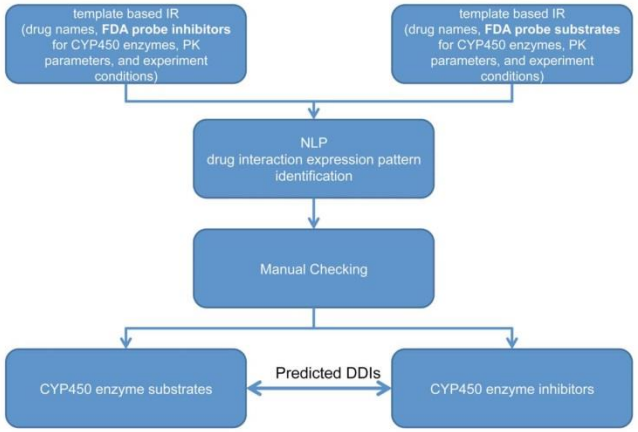
A.V.Lyubimov. Encyclopedia of Drug Metabolism and Interactions. First Edition. Wiley, 2012.

POLYPHARMACY CAUSES DDIs

- The most frequent case of DDIs is when the co-administered drugs are substrates, inducers, or inhibitors of the same metabolizing enzyme(s), potentially altering the expected rate of metabolism of one or both compounds. It is particular case of pharmacokinetic DDI.

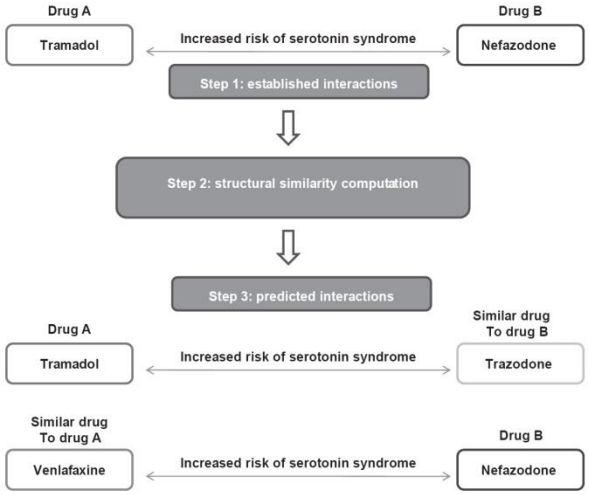
IN SILICO APPROACHES

Literature Based



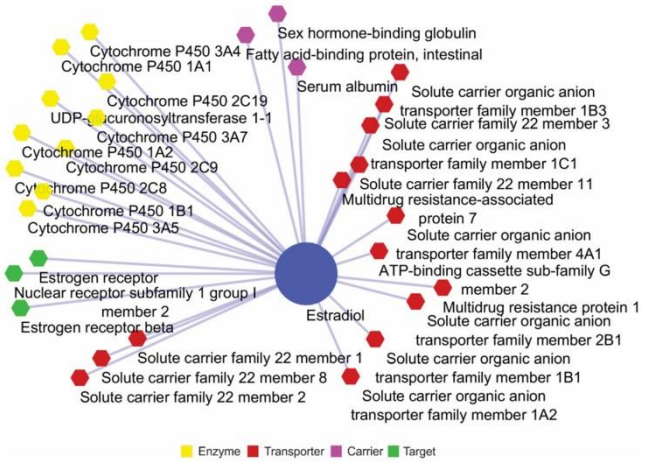
(Duke J., et al., 2012)

Structure similarity



(Vilar S., et al., 2012)

Functional similarities



(Ferdousi R., et al., 2017)

Results of prediction with using of these methods:

- particular prediction for several pairs of drugs under the narrow interest;
- opened databases that contain a bulk of information about predicted DDIs between drugs but without any assessment of severity of manifestation of possible DDIs.

Our goal was to create simple and robust method to predict DDIs severity for the pairs of substances on the base of their structural formulas.

SEVERITY OF DDI

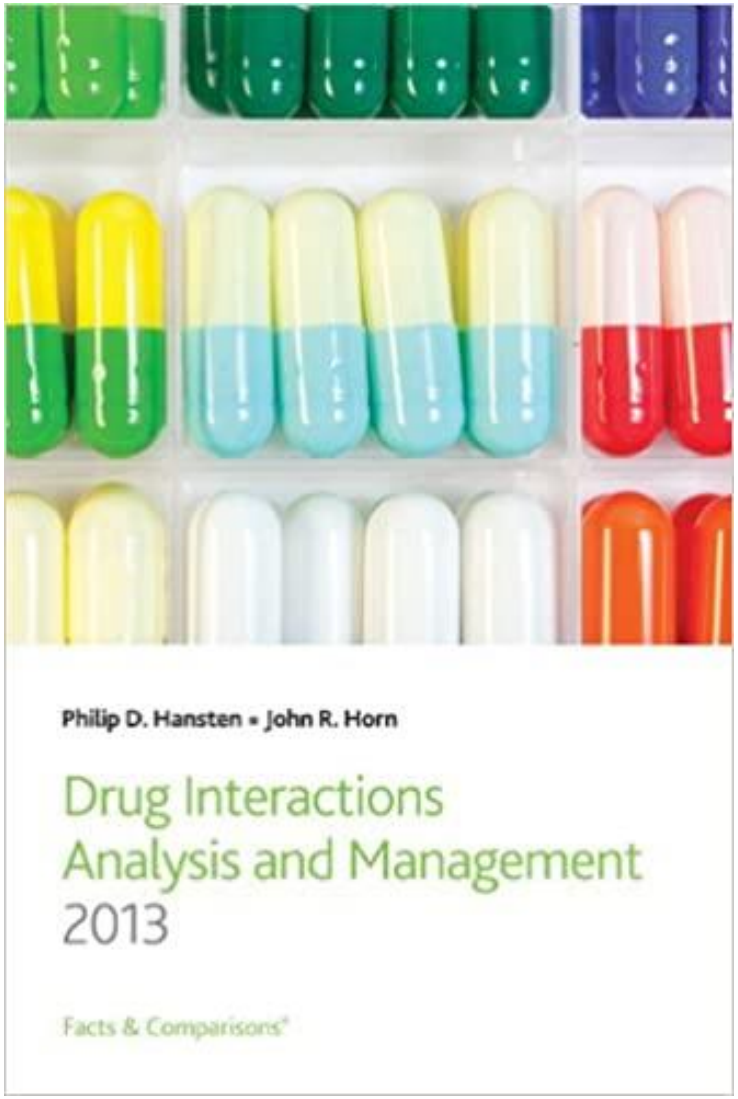
OpeRational ClassificAtion (ORCA) system for the classification of DDIs, created for physicians to assess the risk of co-administration of two drugs. ORCA divides DDI into five classes: contraindicated (class 1), provisionally contraindicated (class 2), conditional (class 3), minimal risk (class 4), no interaction (class 5).

Table 1. OpeRational ClassificAtion (ORCA) System for Classifying Drug Interactions

Class	Description	Examples
1: Contraindicated	No situations have been identified where the benefit of the combination outweighs the risk.	*Monoamine oxidase inhibitor + pseudoephedrine:* The risk (a life-threatening hypertensive reaction) is unacceptable given the potential benefit (possible improvement in cold symptoms).
2: Provisionally Contraindicated	The combination increases the risk of adverse effects. Avoid concurrent use unless interaction is desired or no alternative is available. If the combination is used, increased monitoring may be necessary.	*Warfarin + aspirin:* Acceptable if aspirin is used intentionally as an anticoagulant after evaluation of benefits and risks; not acceptable if aspirin is used for another purpose, such as for pain or fever. *Clarithromycin + carbamazepine:* The risk of carbamazepine toxicity is substantial; if possible, use an alternative macrolide, such as azithromycin or dirithromycin.
3: Conditional	Risk may be increased, depending on the clinical situation. Assess risk and take action as needed.	*Ciprofloxacin + antacids:* Binding in the gastrointestinal tract can be minimized by giving ciprofloxacin 2 hours before or 6 hours after antacid. *Warfarin + thyroid:* Risk is minimal if warfarin started in patients stabilized on thyroid. Monitor clotting status any time a change in clinical thyroid status occurs.
4: Minimal Risk	Risk of adverse outcome appears small. No special precautions appear necessary.	*Caffeine + oral contraceptives:* Serum caffeine concentrations may increase somewhat, but adverse effects are unlikely.
5: No Interaction	Evidence suggests that drugs do not interact.	*Cyclosporine + ofloxacin:* Ofloxacin does not appear to affect cyclosporine pharmacokinetics.

Hansten P.D., Horn J.R., Hazlet T.K. (2001). ORCA: OpeRational ClassificAtion of drug interactions. J. Am. Pharm. Assoc. (Wash). 41(2):161-165.

SEVERITY OF DDI



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The primary information source for creation of the training set was the handbook for physicians "Drug Interaction Analysis and Management 2013 Eighth Edition".
All the cases of DDI mentioned in the handbook belong to classes 1-5 of ORCA classification.

TRAINING SET

- We collected the data contained information about 2090 pairs of drugs, which belong to class 1 (59), class 2 (236), class 3 (1139), class 4 (523) and class 5 (133) of DDI in case of co-administration.

- The majority of the drugs associated with drug-drug interactions in data set are targeted on nervous and cardiovascular systems or anti-infective agents.

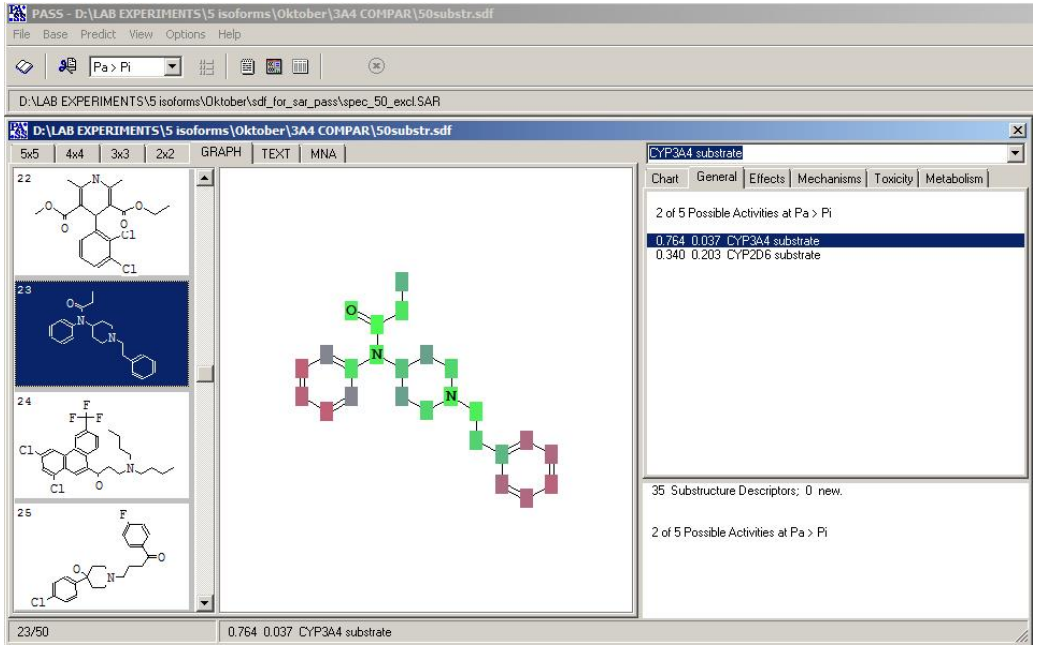
- It was found that CYP3A4 plays a major role in drug-drug interactions, which corresponds to the published data.

METHODS AND ALGORITHMS

The prediction of DDI classes is based on a combination of modified substructural MNA descriptors - **PoSMNA**, and a classification algorithm implemented in the **PASS** software.

PASS

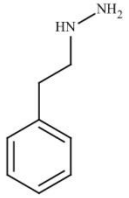
Prediction of Activity Spectra for Substances software

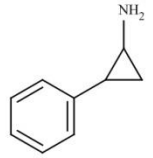


PoSMNA

Pairs of Substances

Multilevel Neighborhoods of Atoms





C(C(CC-H)C(CC-H)-H(C))
C(C(CC-H)C(CC-H)-C(C-H-H-C))
C(C(CC-H)C(CC-C)-H(C))
-C(C(CC-C)-H(-C)-H(-C)-C(-H-H-C-N))
-C(-H(-C)-H(-C)-C(C-H-H-C)-N(-H-C-N))
-N(-H(-N)-H(-N)-N(-H-C-N))
-N(-H(-N)-C(-H-H-C-N)-N(-H-H-N))

Phenelzine

C(C(CCC-H)C(CC-H-H)-H(C)-N(C-H-H))
C(C(CCC-H)C(CC-H-N)-H(C)-H(C))
C(C(CCC-H)C(CC-H)C(CC-H))
C(C(CCC)C(CC-H-H)C(CC-H-N)-H(C))
C(C(CCC)C(CC-H)-H(C))
C(C(CC-H)C(CC-H)-H(C))
-N(C(CC-H-N)-H(-N)-H(-N))

Tranylcypromine

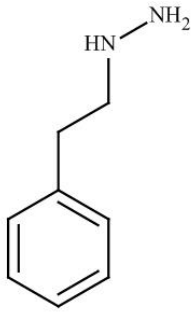
C(C(CC-H)C(CC-H)-H(C)) C(C(CCC-H)C(CC-H-H)-H(C)-N(C-H-H))
C(C(CC-H)C(CC-H)-H(C)) C(C(CCC-H)C(CC-H-N)-H(C)-H(C))
C(C(CC-H)C(CC-H)-H(C)) C(C(CCC-H)C(CC-H)C(CC-H)

. . .

-N(-H(-N)-C(-H-H-C-N)-N(-H-H-N)) C(C(CCC)C(CC-H)-H(C))
-N(-H(-N)-C(-H-H-C-N)-N(-H-H-N)) C(C(CC-H)C(CC-H)-H(C)
-N(-H(-N)-C(-H-H-C-N)-N(-H-H-N)) -N(C(CC-H-N)-H(-N)-H(-N))

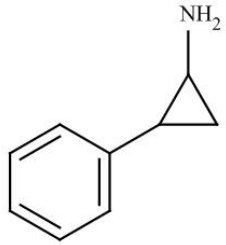
The output file represents a list of DDI ORCA classes with two probabilities **Pa -** probability for the pair of compounds to belong to the particular class of DDI and **Pi** - probability of the opposite.

MNA
(Multilevel Neighbourhoods of Atoms)



C(C(CC-H)C(CC-H)-H(C))
C(C(CC-H)C(CC-H)-C(C-H-H-C))
C(C(CC-H)C(CC-C)-H(C))
-C(C(CC-C)-H(-C)-H(-C)-C(-H-H-C-N))
-C(-H(-C)-H(-C)-C(C-H-H-C)-N(-H-C-N))
-N(-H(-N)-H(-N)-N(-H-C-N))
-N(-H(-N)-C(-H-H-C-N)-N(-H-H-N))

Phenelzine



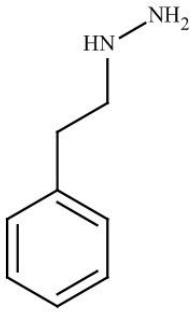
C(C(CCC-H)C(CC-H-H)-H(C)-N(C-H-H))
C(C(CCC-H)C(CC-H-N)-H(C)-H(C))
C(C(CCC-H)C(CC-H)C(CC-H))
C(C(CCC)C(CC-H-H)C(CC-H-N)-H(C))
C(C(CCC)C(CC-H)-H(C))
C(C(CC-H)C(CC-H)-H(C))
-N(C(CC-H-N)-H(-N)-H(-N))

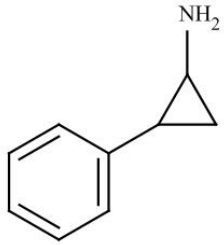
Tranylcypromine

The structure of the molecule for DDI analysis is represented as a set of MNA descriptors (Multilevel Neighborhoods of Atoms) of the 2nd-levels only for heavy atoms.
In DDI, a pair of molecules is represented as a set of the PoSMNA descriptors (Pair of Substances MNA).

The set of PoSMNA descriptors is the direct product of two sets of MNA descriptors for each molecule in the DDI pair as {**a,b,c,…**}X{**d,e,f,…**} = {**ad,ae,af,…, bd,be,bf,…, cd,ce,cf,…**}

PoSMNA (Pairs of Substances Multilevel Neighbourhoods of Atoms)





C(C(CC-H)C(CC-H)-H(C))
C(C(CC-H)C(CC-H)-C(C-H-H-C))
C(C(CC-H)C(CC-C)-H(C))
-C(C(CC-C)-H(-C)-H(-C)-C(-H-H-C-N))
-C(-H(-C)-H(-C)-C(C-H-H-C)-N(-H-C-N))
-N(-H(-N)-H(-N)-N(-H-C-N))
-N(-H(-N)-C(-H-H-C-N)-N(-H-H-N))

C(C(CCC-H)C(CC-H-H)-H(C)-N(C-H-H))
C(C(CCC-H)C(CC-H-N)-H(C)-H(C))
C(C(CCC-H)C(CC-H)C(CC-H))
C(C(CCC)C(CC-H-H)C(CC-H-N)-H(C))
C(C(CCC)C(CC-H)-H(C))
C(C(CC-H)C(CC-H)-H(C))
-N(C(CC-H-N)-H(-N)-H(-N))

multiplication of two descriptors

C(C(CC-H)C(CC-H)-H(C)) C(C(CCC-H)C(CC-H-H)-H(C)-N(C-H-H))
C(C(CC-H)C(CC-H)-H(C)) C(C(CCC-H)C(CC-H-N)-H(C)-H(C))
C(C(CC-H)C(CC-H)-H(C)) C(C(CCC-H)C(CC-H)C(CC-H)

-N(-H(-N)-C(-H-H-C-N)-N(-H-H-N)) C(C(CCC)C(CC-H)-H(C))
-N(-H(-N)-C(-H-H-C-N)-N(-H-H-N)) C(C(CC-H)C(CC-H)-H(C)
-N(-H(-N)-C(-H-H-C-N)-N(-H-H-N)) -N(C(CC-H-N)-H(-N)-H(-N))

RESULTS

DDIs Class	N	DDIs IAP	DDIs IAP 20-Fold
Class 1	59	0.876	0.876
Class 2	236	0.788	0.777
Class 3	1139	0.683	0.679
Class 4	523	0.671	0.668
Class 5	133	0.752	0.754
Average		**0.754**	**0.751**

The average AUC, calculated in the leave-one-out cross-validation procedure, was about 0.75

http://way2drug.com/ddi/

Way2Drug PREDICTIVE SERVICES
Understanding Chemical-Biological Interactions

DDI-Pred: web-service for drug-drug interaction prediction
Supported by the Russian Science Foundation (project no. 17-75-20250)

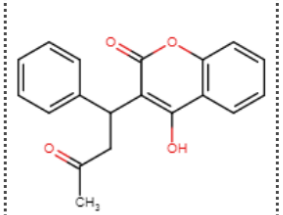
» Home | » Training Sets | » Products/Services | » Interpretation | » Contacts

Input SMILES
Input drug name
Draw Structure
View/Hide result

Amiodarone
Add structure
Examples: Ampicillin

Clear data

#1 Delete Select



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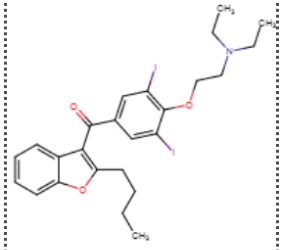

Get DDI data

You have selected compounds: 1;2

CYP1A2-inactive(in AD)
CYP2C9-active(in AD)
CYP2D6-active(in AD)
CYP3A4-active(in AD)

DDI Class (performed by PASS program)

CLASS 1

DDI, based on activity (performed by PASS program)

Pa-Pi= 0.7
anti-infectives-Inactive
cardiovascular-Inactive
nervous-Inactive

Summary

- Training set with DDIs described by OpeRational ClassificAtion (ORCA) system was used.
- Special PoSMNA descriptors for the pairs of substances were created.
- The average AUC was about 0.75.
- DDI severity prediction using PASS approach and specially created descriptors can be applied to solving practical problems.
- The pilot version of the freely available web resource dedicated to the DDI prediction (http://way2drug.com/ddi/) was created.

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Thank you for your attention!

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More details in article https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6864873/
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