Classification of Adverse Drug Reactions

Term Project

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General Information / Adverse Drug Reactions

- ADRs are harmful or unpleasant reactions to a medication or other therapeutic intervention that are based on a variety of factors:

1. Patient-related factors:
   age, gender, weight, genetics,

2. Route of administration:
   intravenous vs oral administration etc.

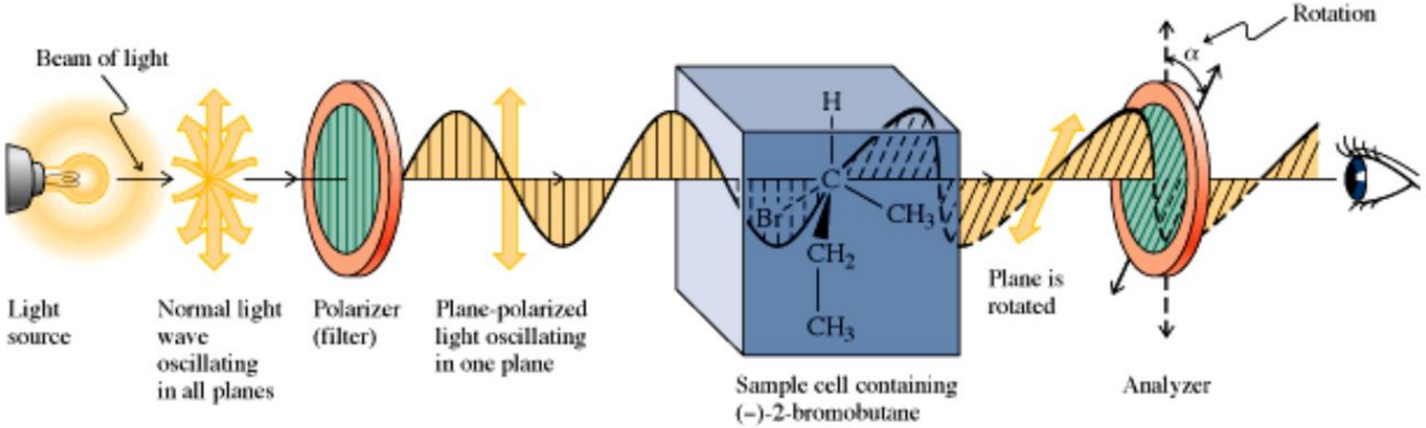
3. Environmental factors:
   exposure to toxins, pollutants, or other chemicals

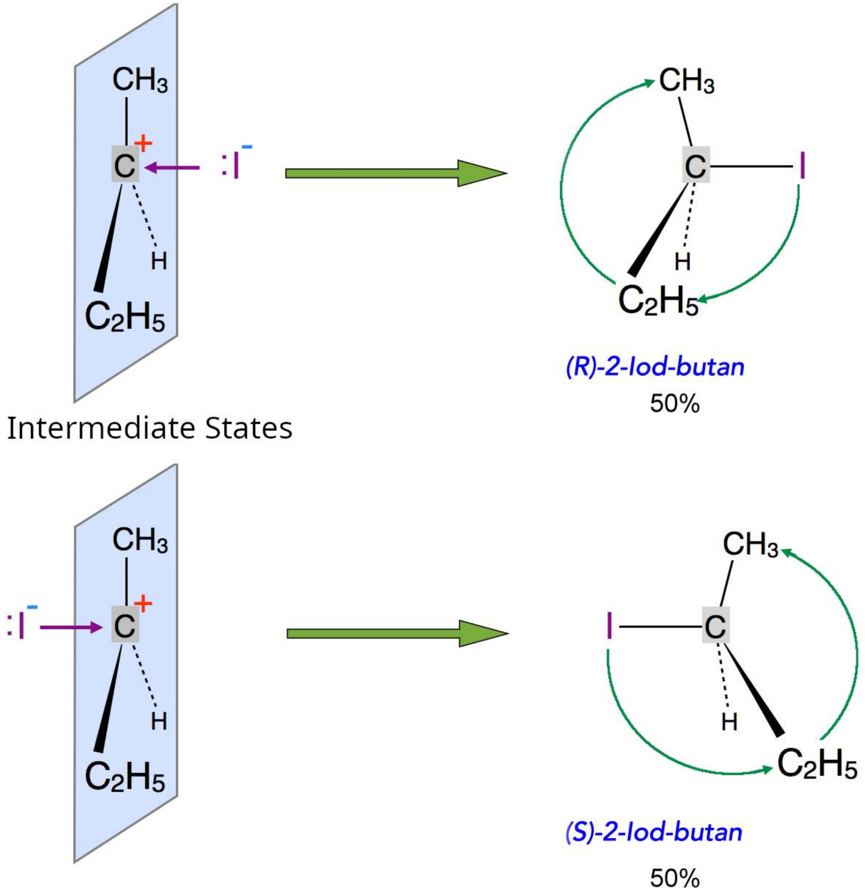
4. Drug-related factors:
   drug dosage, drug interactions, duration of use, **stereochemistry**

- Carbon that is bound to 4 different atoms is considered as chirality center

- (R)/(S) forms of compounds are called enatiomers

> Different chemical properties



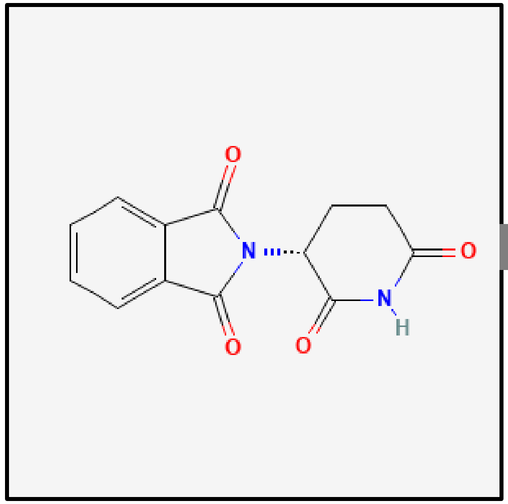


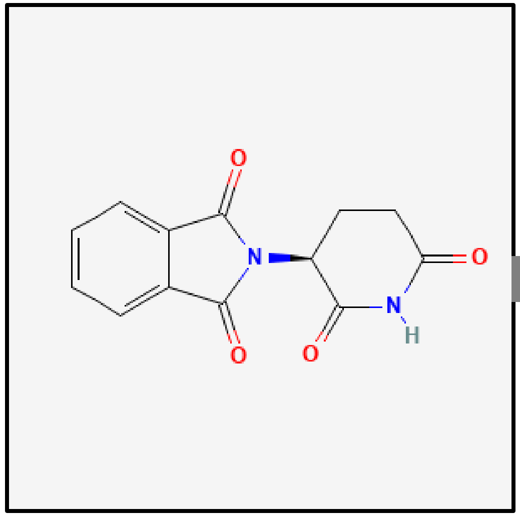
Racemat

General Information / Stereochemistry

The Thalidomide Scandal:

- Medical compound developed for treating anxiety trouble sleeping, tension and morning sickness
- Considered as safe for pregnant women even though not clinically tested





(R)-Thalidomide

50:50
Racemat

(S)-Thalidomide

General Information / SMILES

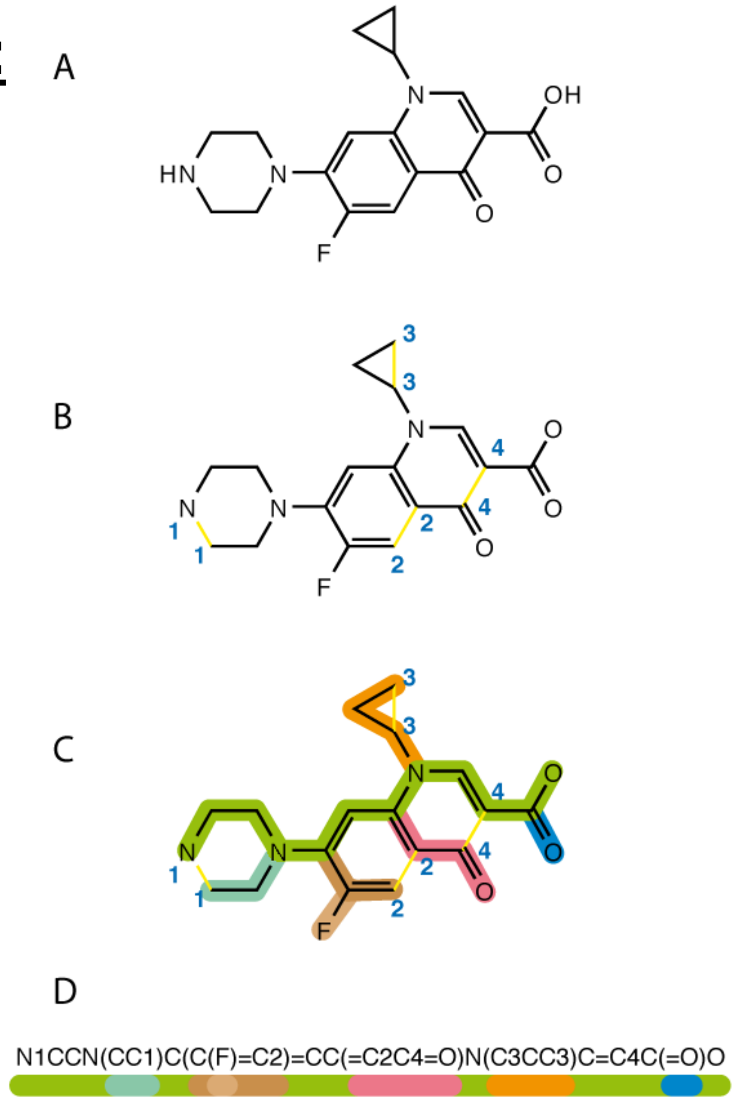
<u>Simplified molecular-input line-entry system (SMILES):</u>

<u>(+)-Thalidomide:</u>

C1CC(=O)NC(=O)C1N2C(=O)C3=CC=CC=C3C2=O

<u>(-)-Thalidomide:</u>

C1CC(=O)NC(=O)C1N2C(=O)C3=CC=CC=C3C2=O



General Information / SMILES

Simplified molecular-input line-entry system (SMILES):

(+)-Thalidomide:

C1CC(=O)NC(=O)C1N2C(=O)C3=CC=CC=C3C2=O

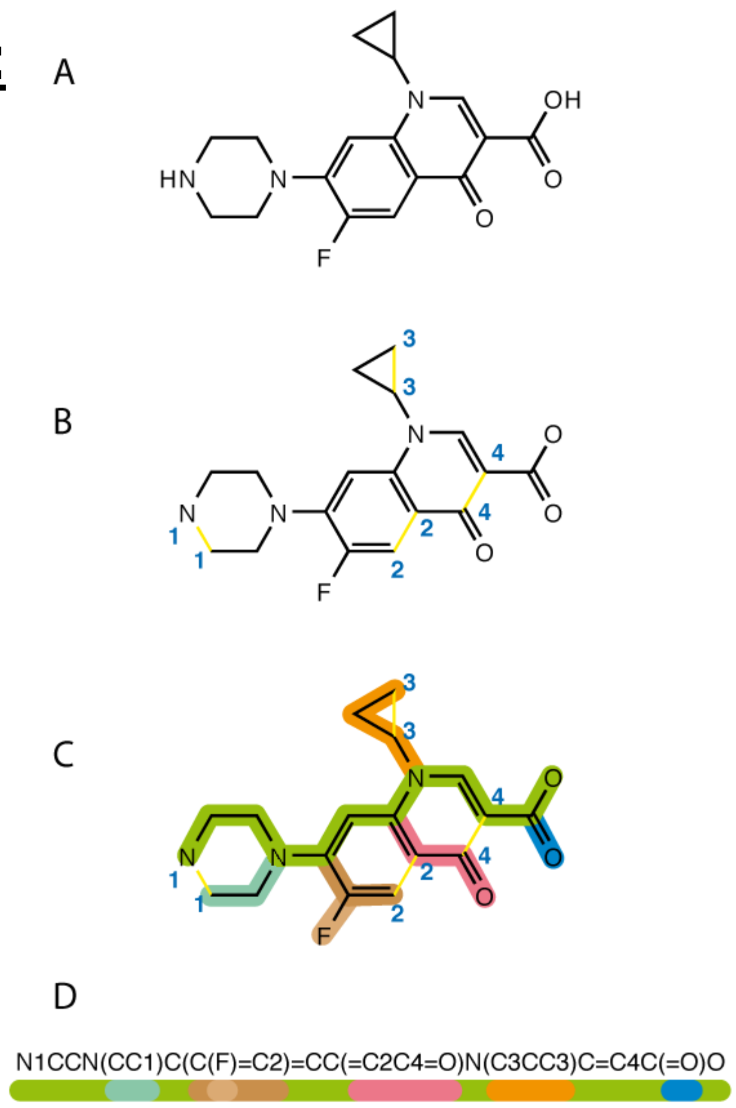
C1CC(=O)NC(=O)[C@@H]1N2C(=O)C3=CC=CC=C3C2=O

(-)-Thalidomide:

C1CC(=O)NC(=O)C1N2C(=O)C3=CC=CC=C3C2=O

C1CC(=O)NC(=O)[C@H]1N2C(=O)C3=CC=CC=C3C2=O

> Isomeric SMILES



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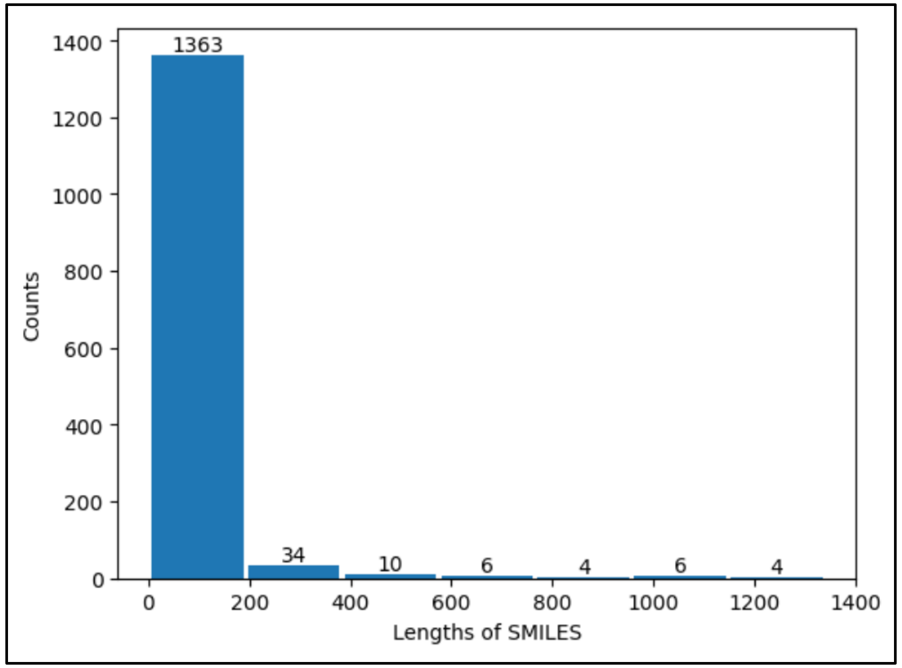
Data / SIDER data set

- SIDER contains information on marketed medicines and their recorded adverse drug reactions
- More comprehensive data set available via DeepChem:

>1427 medical compounds with 27 distinct binary labeled ADRs



smiles	Hepatobiliary disorders	Metabolism and nutrition disorders	Product issues	Eye disorders	Investigations	Musculoskeletal and connective tissue disorders	Gastrointestinal disorders
C(CNCCNCCNCCN)N	1	1	0	0	1	1	1
CC(C)(C)C1=CC(=C(C=C1NC(=O)C2=CNC3=CC=CC=C3C2=...	0	1	0	0	1	1	1
CC[C@]12CC(=C)[C@H]3[C@H]([C@@H]1CC[C@]2(C#C)O...	0	1	0	1	1	0	1
CCC12CC(=C)C3C(C1CC[C@]2(C#C)O)CCC4=CC(=O)CCC34	1	1	0	1	1	1	1
C1C(C2=CC=CC=C2N(C3=CC=CC=C31)C(=O)N)O	1	1	0	1	1	1	1

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Aims & Problems

Aim: train the best possible classifier to predict ADRs

Problems:

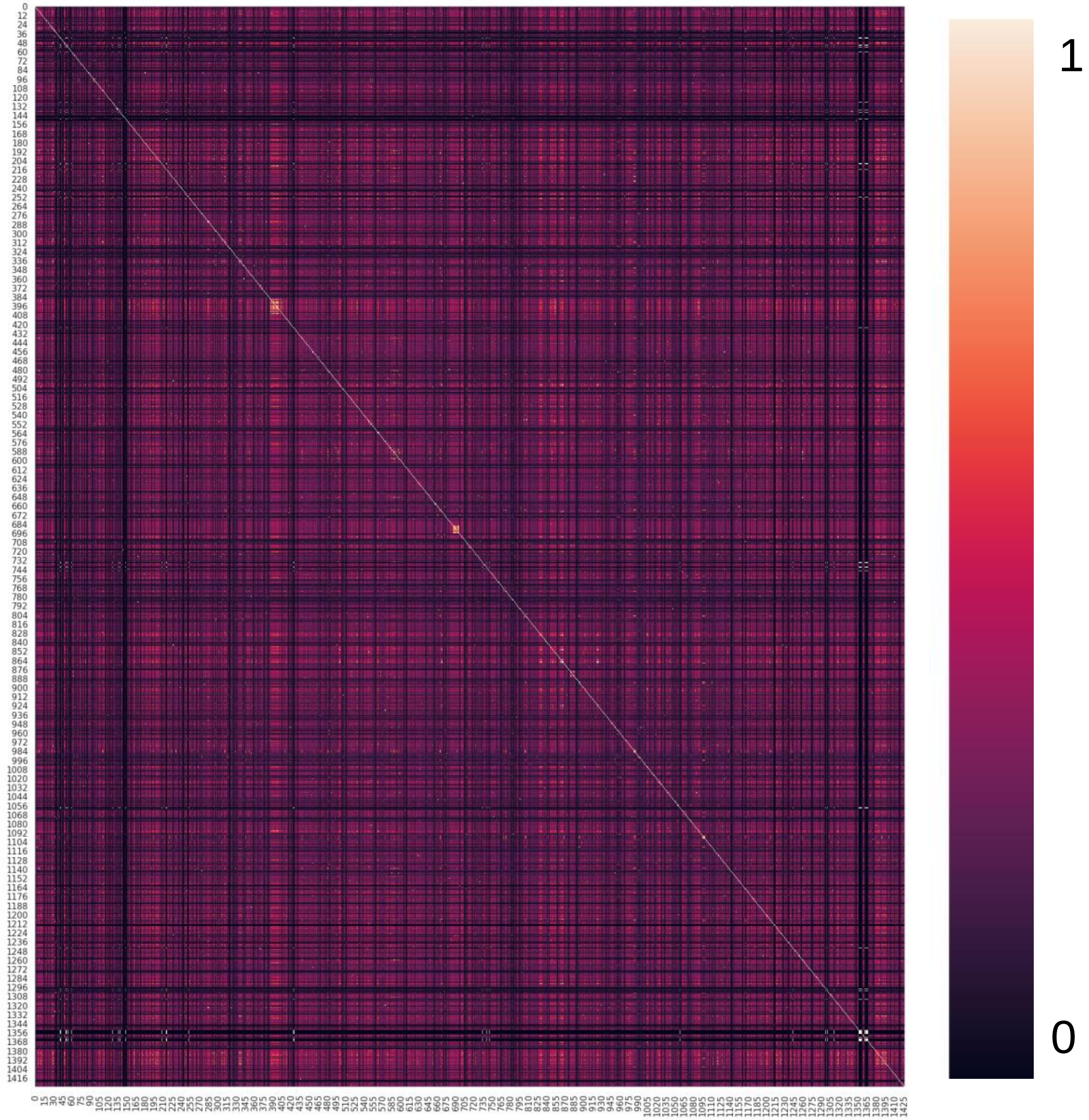
- Numerical representation of SMILES
- Class Imbalance

Aims & Problems

- Tanimoto coefficient: Measures the structural similarity between molecules

- SIDER molecules show generally a strong structural correlation

> One-hot-encoding not suitable



Aims & Problems

- NLP technique
- Word embedding = representation of a word
- Result is typically a real valued vector
- Captures similarity

Aims & Problems

- Class imbalance if the ratio of samples in the minority class is much lower than the ratio of majority class
  > Synthetic Minority Oversampling Technique (SMOTE)
  > Duplicate samples from the minority class

ADR	Negative count	Positive count	Count difference	Minority ratio	Majority ratio	Ratio difference
Hepatobiliary disorders	684	743	59	48	52	4
Metabolism and nutrition disorders	431	996	565	30	70	40
Product issues	1405	22	1383	2	98	96
Eye disorders	551	876	325	39	61	22
Investigations	276	1151	875	19	81	62
Musculoskeletal and connective tissue disorders	430	997	567	30	70	40

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WE Network / Preprocessing

SMILES (string)

['C1=CC(C(C(=C1)C(=O)O)O)O']

> input

SMILES Pair Encoding (list of strings)

['C1=', 'CC(', 'C(', 'C(=', 'C1)', 'C(=O)O)', 'O)', 'O']

> structural groups

Keras Tokenizer

{'c1=':1, 'cc(':2, 'c(':3, 'c(=':4, 'c1)':5, 'c(=o)o)':6, 'o)':7, 'o':8}

> vocabulary based on word frequency

[[1, 2, 3, 4, 5, 6, 7, 8]]

> **padded numerical SMILES representation based on structural groups**

WE Network / Training Data

- Train a word embedding network for finding structural patterns / correlations

Training Data

~ 440k isomeric SMILES from PubChem

Preprocessing

SMILES (string)

['C1=CC(C(C(=C1)C(=O)O)O)O']

> input

SMILES Pair Encoding (list of strings)

['C1=', 'CC(', 'C(', 'C(=', 'C1)', 'C(=O)O)', 'O)', 'O']

> structural groups

Keras Tokenizer

{'c1=':1, 'cc(':2, 'c(':3, 'c(=':4, 'c1)':5, 'c(=o)o)':6, 'o)':7, 'o':8}

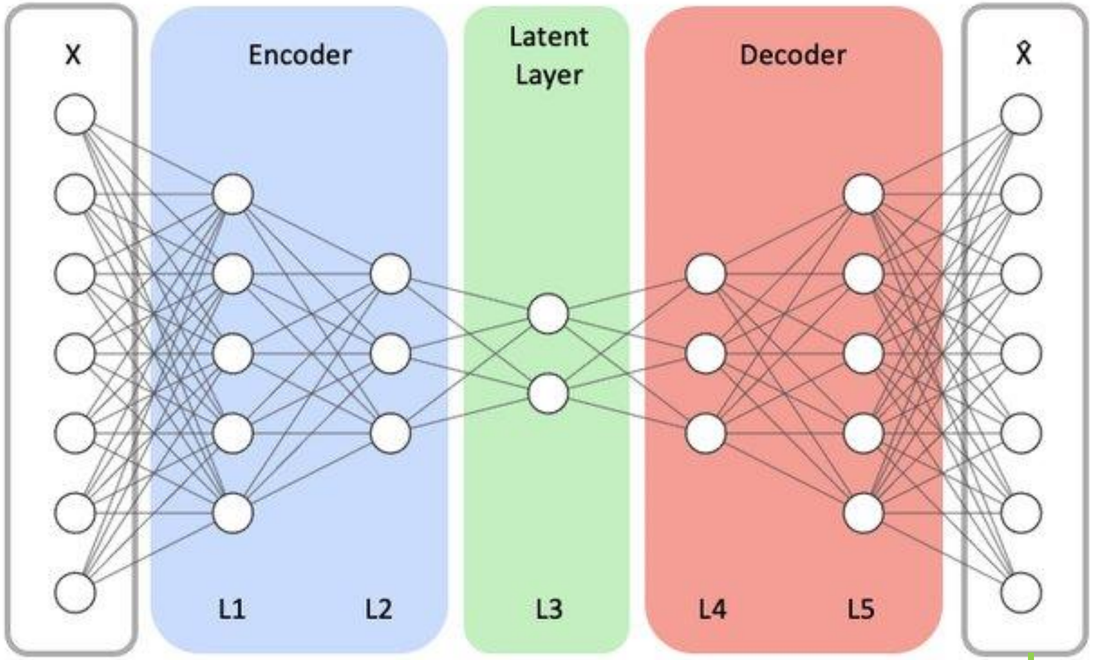
> vocabulary based on word frequency

[[1, 2, 3, 4, 5, 6, 7, 8]]

> padded numerical SMILES representation based on structural groups

Vectors (358,)

Word Embedding (WE) Network



Feedback

> floating vector with 50 entries for each SMILE

WE Network / Encoder

```
Model: "we_encoder"
_________________________________________________________________
 Layer (type)                Output Shape              Param #
=================================================================
 encoder_input (InputLayer)  [(None, 358)]             0

 encoder_embedding (Embeddin  (None, 358, 50)          102400
 g)

 encoder_rnn (Bidirectional)  (None, 358, 256)         628736

 encoder_avg_pool (GlobalAve  (None, 256)              0
 ragePooling1D)

 encoder_fc_dense_1 (Dense)  (None, 256)               65792

 encoder_fc_dense_2 (Dense)  (None, 256)               65792

 encoder_output (Dense)      (None, 50)                12850

=================================================================
Total params: 875,570
Trainable params: 875,570
Non-trainable params: 0
_________________________________________________________________
```

Encoder

> generates a WE from preprocessed SMILE

WE Network / Decoder

```
Model: "we_decoder"
_________________________________________________________________
 Layer (type)                Output Shape              Param #
=================================================================
 decoder_input (InputLayer)  [(None, 50)]              0

 decoder_fc_dense_1 (Dense)  (None, 50)                2550

 decoder_fc_dense_2 (Dense)  (None, 256)               13056

 decoder_fc_dense_3 (Dense)  (None, 256)               65792

 decoder_output (Dense)      (None, 358)               92006

=================================================================
Total params: 173,404
Trainable params: 173,404
Non-trainable params: 0
_________________________________________________________________
```

Decoder

> Takes word embedding created by the encoder

> Tries to reconstruct back the initial SMILE

WE Network / Architecture

```
Model: "we_network"
_________________________________________________________________
 Layer (type)                Output Shape              Param #
=================================================================
 encoder_input (InputLayer)  [(None, 358)]             0

 encoder_embedding (Embeddin  (None, 358, 50)          102400
 g)

 encoder_rnn (Bidirectional)  (None, 358, 256)         628736

 encoder_avg_pool (GlobalAve  (None, 256)              0
 ragePooling1D)

 encoder_fc_dense_1 (Dense)  (None, 256)               65792

 encoder_fc_dense_2 (Dense)  (None, 256)               65792

 encoder_output (Dense)      (None, 50)                12850

 we_decoder (Functional)     (None, 358)               173404

=================================================================
Total params: 1,048,974
Trainable params: 1,048,974
Non-trainable params: 0
_________________________________________________________________
```

Autoencoder

> Comprise both models into one network

> capture semantics of SMILE and return word embeddings

> Only Encoder part of the Autoencoder model is needed for generation of Word Embeddings

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Classifier

Vectors (358,)

Vectors (50,)

Training Data

SIDER Dataset (1427,28)

Preprocessing

SMILES (string)

['C1=CC(C(C(=C1)C(=O)O)O)O']

> input

SMILES Pair Encoding (list of strings)

['C1=', 'CC(', 'C(', 'C(=', 'C1)', 'C(=O)O)', 'O)', 'O']

> structural groups

Keras Tokenizer

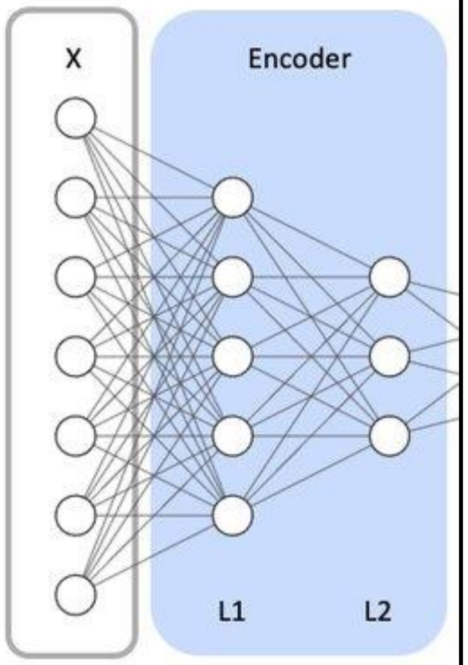
{'c1=':1, 'cc(':2, 'c(':3, 'c(=':4, 'c1)':5, 'c(=o)o)':6, 'o)':7, 'o':8}

> vocabulary based on word frequency

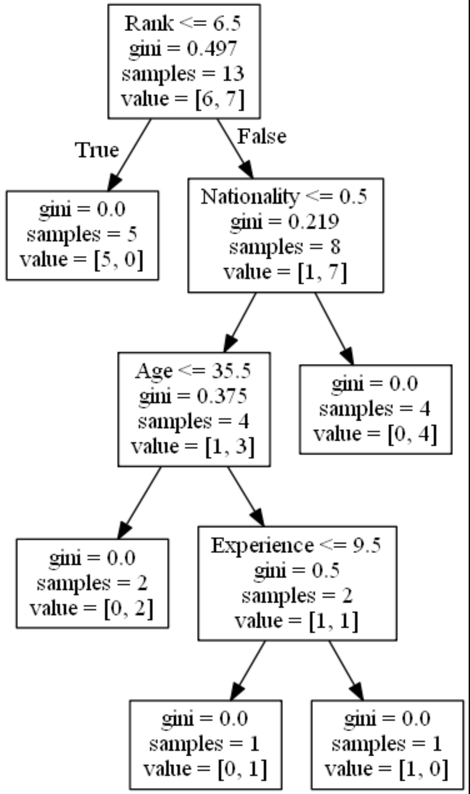
[[1, 2, 3, 4, 5, 6, 7, 8]]

> padded numerical SMILES representation based on structural groups

Pretrained Encoder



Decision Tree



AdaBoost

ADR Prediction

Classifier / Results

Decision Tree

ADR	Accuracy score	F1 score
Hepatobiliary disorders	64 %	58 %
Metabolism and nutrition disorders	98 %	98 %
Product issues	59 %	53 %
Eye disorders	75 %	75 %
Investigations	62 %	62 %
Musculoskeletal and connective tissue disorders	78 %	78 %
Gastrointestinal disorders	73 %	77 %
Social circumstances	64 %	70 %
Immune system disorders	68 %	75 %
Reproductive system and breast disorders	87 %	85 %
Neoplasms benign, malignant and unspecified (i...	70 %	72 %
General disorders and administration site cond...	70 %	72 %
Endocrine disorders	68 %	73 %
Surgical and medical procedures	56 %	67 %
Vascular disorders	87 %	86 %
Blood and lymphatic system disorders	64 %	61 %
Skin and subcutaneous tissue disorders	70 %	73 %
Congenital, familial and genetic disorders	71 %	67 %
Infections and infestations	62 %	64 %
Respiratory, thoracic and mediastinal disorders	63 %	66 %
Psychiatric disorders	86 %	87 %
Renal and urinary disorders	66 %	61 %
Pregnancy, puerperium and perinatal conditions	81 %	82 %
Ear and labyrinth disorders	58 %	57 %

Decision Tree + AdaBoost

ADR	Accuracy score	F1 score
Hepatobiliary disorders	76 %	71 %
Metabolism and nutrition disorders	100 %	100 %
Product issues	66 %	64 %
Eye disorders	85 %	84 %
Investigations	77 %	73 %
Musculoskeletal and connective tissue disorders	95 %	95 %
Gastrointestinal disorders	88 %	90 %
Social circumstances	80 %	78 %
Immune system disorders	83 %	85 %
Reproductive system and breast disorders	94 %	93 %
Neoplasms benign, malignant and unspecified (i...	83 %	85 %
General disorders and administration site cond...	90 %	91 %
Endocrine disorders	81 %	80 %
Surgical and medical procedures	69 %	68 %
Vascular disorders	95 %	95 %
Blood and lymphatic system disorders	88 %	90 %
Skin and subcutaneous tissue disorders	77 %	75 %
Congenital, familial and genetic disorders	83 %	82 %
Infections and infestations	75 %	73 %
Respiratory, thoracic and mediastinal disorders	72 %	69 %
Psychiatric disorders	93 %	93 %
Renal and urinary disorders	78 %	75 %
Pregnancy, puerperium and perinatal conditions	94 %	94 %
Ear and labyrinth disorders	72 %	68 %

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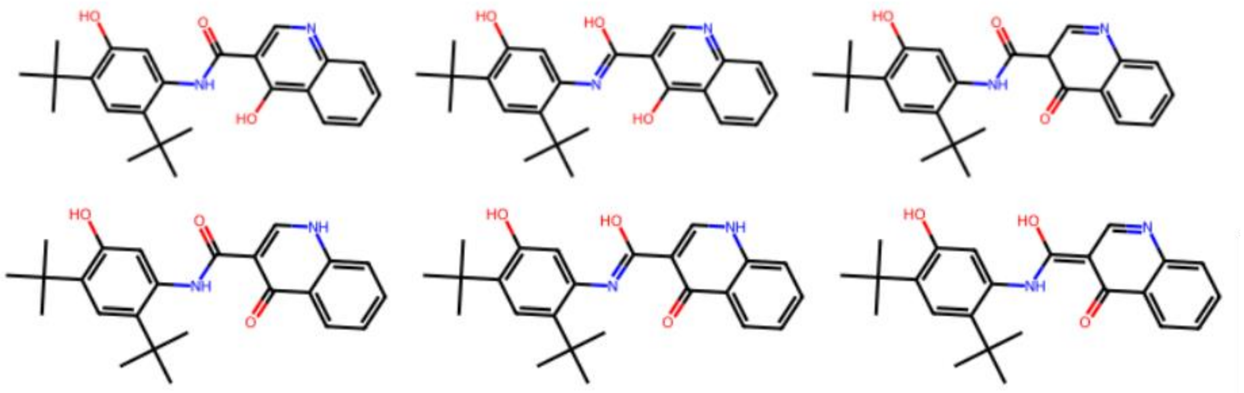
Discussion

- Data Augmentation:
  > Creating tautomeric structures
  from SIDER SMILES



- Better Word Embedding Network

- Using Graph Embeddings

- More comprehensive dataset with better covering of the dynamics of ADRs

Thank you for your Attention!

&

Don’t f**o**rget t**o** SMILE

C1[C@H](SC(=C(C#N)N2C=CN=C2)S1)C3=C(C=C(C=C3)Cl)Cl

Sources

- **Pictures:**

https://www.welt.de/geschichte/article169174727/Wie-die-Atombombe-gegen-Contergan-blind-machte.html
https://www.welt.de/kultur/history/article108632744/Der-Kampf-der-Contergan-Firma-gegen-die-Opfer.html
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https://en.wikipedia.org/wiki/File:SMILES.png
https://www.u-helmich.de/che/Sek2/Organik/Mechanismen/SN/Bilder/SN1-02.jpg
https://www.uibk.ac.at/organic/micura/teaching/grundlagen-organische-chemie/download/ocphkap6.pdf
https://www.w3schools.com/python/python_ml_decision_tree.asp

- **Data Sources:**

Drug components with annotated ADRs
https://deepchemdata.s3-us-west-1.amazonaws.com/datasets/sider.csv.gz

Isomeric SMILES for WE-network training
https://ftp.ncbi.nlm.nih.gov/pubchem/Compound/CURRENT-Full/SDF/

- **Software**

https://pypi.org/project/SmilesPE/

https://github.com/jurajtrappl/adverse-drug-reactions