Feature combinations networks with statistical (Q)SAR models: interpretation and knowledge mining

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Who is Lhasa

• Not-for-profit organisation
• Data sharing initiatives
• Software for *in silico* prediction of:
  • Toxicity: Derek & Sarah Nexus
  • Metabolism: Meteor Nexus
  • Degradation: Zeneth
• Data sharing initiatives:
  • Toxicity database: Vitic Nexus
  • Pre-competitive data sharing initiatives: aromatic amines, intermediates…
What is this presentation about?

• Interpretation of *in silico* predictions
  • What is an interpretation?
  • Why do we want an interpretation?
  • What are the current limitations?

• How do we get an interpretation
  • Literature published algorithms
  • Feature combination networks algorithm
  • Interpretation to knowledge mining…
Model purpose

• To predict the target activity or property of a previously unseen structure

• In this presentation we will be considering the specific case of binary activity predictions
(Q)SAR / (Q)SPR modelling

• Take a dataset
• Build a model
• Make a prediction

There can be a disconnect between the purpose the model is being built for and concerns of the modeller.
(Q)SAR / (Q)SPR modelling

- Take a dataset
- Build a model
- Make a prediction

Focus of the modeller

Focus of the user

The requirements/interests of a user may differ depending on the use case the model is required for.

Two main points:

1) Prediction: accuracy is important

2) Understanding: accuracy and interpretation are important
(Q)SAR / (Q)SPR modelling

• Take a dataset
• Build a model
• Make a prediction

If accuracy is key and we may not require an interpretation (batch processing / screening / scoring) then the modeller may be able to limit the concerns over the interpretability of a particular learning algorithm.
(Q)SAR / (Q)SPR modelling

- Take a dataset
- Build a model
- Make a prediction

If interpretation is important the modeller may be more constrained in terms of choice of descriptors and algorithm.

In some cases a poorer performing model may be chosen for its interpretation.
What constitutes an interpretation?

• The model provides a prediction
  • This structure is predicted to be mutagenic
• The ability of the model to explain the prediction is the first step
  • This structure is predicted to be mutagenic due to the structural motif X
• The ability to link the explanation of the prediction to the domain being modelled
  • Structural motif X is an alkylating agent which is an electrophilic species capable of directly alkylating DNA
What limits an interpretation?

• The learning algorithm used:
  • White box models give an explanation for the prediction
  • Black box models do not provide an explanation for the prediction

• The descriptors used:
  • If the descriptors are not intelligible the prediction can’t be either
  • If too many descriptors are used even interpretable learning algorithms become uninterpretable

• Machine learning generally does not provide a mechanistic reasoning
  • Given sufficient choice in descriptors and a method of identifying a cause in the prediction the user can be supported in forming a mechanistic reason
What limits an interpretation?

• Decision tree:
  • **White box**: path through the tree provides the cause of the prediction
    • Requires careful choice in descriptor!

• kNN:
  • **White box (?)**: nearest neighbours can be shown and weights indicated
    • Subjective, doesn’t indicate the impact of structural features

• Random Forest:
  • **Black box**: global importance measures do not provide sufficient detail to understand the cause of a specific prediction

• Neural network, Support Vector Machine:
  • **Black box**: requires post processing to elucidate the cause of the prediction
What limits an interpretation?

• Why not just use a white box learning algorithm?
  • In practice the performance of the white box algorithms is often lower than that of the black box algorithms

• Why not just use an expert system?
  • Time consuming to develop expert knowledge and encode in a predictive system – not always the desirable choice
  • Interpretation algorithms can be combined with machine learning algorithms to support the development of expert systems
Why do we want an interpretation?

• When we know why a prediction has been made we are a step further to:
  • Mitigate negative effects
  • Improve positive effects
  • Can allow an expert to challenge or accept a prediction

• We want this interpretation without a loss in performance:
  • Add an interpretation to black box algorithms
  • Designed to be agnostic to the learning algorithm chosen
EXISTING ALGORITHMS
Existing algorithms

- A variety of approaches for interpretation have been developed
- Often specific to a learning algorithm
- Can be grouped into:
  - Visualisation of relevant training structures
  - Global importance measures
  - Identification of significance of features
  - Identification of behaviour of:
    - Fragments
    - Atoms and bonds
    - Physicochemical properties
Expert systems

• Tell you why a prediction was made
• May provide mechanistic / domain information for the prediction
Identifying the importance of features

- Global ranking of descriptors
  - Can be achieved through descriptor scrambling (such as random forest approach)

- Can be misleading:
  - Sparse features may make an insignificant global impact
  - May not account for combination effects

- Provides broad level information when performed globally

- Can provide fine level information when performed locally with interpretable descriptors
Visualising relevant training structures

• Coarse level interpretation

• Activity not ascribed to a feature, the user is responsible for identifying the cause from the provided examples

• Useful when combined with other approaches
  • Can provide structural analogues
Identifying the behaviour of atoms and fragments

• Aim to assign contribution to a given set of atoms and bonds or a fragment
• Some approaches define the contribution of an entity as the difference between the prediction with the entity and the prediction without

\[ R_i = f(x(f_i = 1)) - f(x(f_i = 0)) \]

Franke et al. feature importance, where \( x \) is a fingerprint with the presence (\( f_i = 1 \)) or absence (\( f_i = 0 \)) of feature \( f_i \).

\( f_i = 3 \) point pharmacophore
Normalise within a given query

Identifying the behaviour of atoms and fragments

- Riniker and Landrum have used a similar approach:
  - The contribution of an atom is the difference between the full fingerprint probability for the active class and the probability of the active class with the contribution of the atom removed
  - [http://www.jcheminf.com/content/5/1/43](http://www.jcheminf.com/content/5/1/43)
  - Available in RDKit

```python
this_fp = calculate_fingerprints(this_mol)
weights = []
orig_proba = predict_model_probabilities(this_fp)
for atom in this_mol.getAtoms():
    new_fp = calculate_fingerprint_without_atom(this_mol, atom)
    new_proba = predict_model_probability(new_fp)
    weight = orig_proba - new_proba
    weights.append(weight)
```

- This interpretation is investigating an atom's contribution to the active class probability
Identifying the behaviour of atoms and fragments

- Polishchuk et al. have developed a similar methodology using fragments instead of atoms

\[ P_{AB}(B) = P_{pred}(AB) - P_{pred}(A) \]

- For binary endpoints a feature can be activating, no contribution or deactivating based on **crossing the class boundary**

- Multiple causes of activity are a problem

\[
\begin{align*}
P_{ABC}(A) &= 1 - 1 = 0 \\
P_{ABC}(B) &= 1 - 1 = 0 \\
P_{ABC}(C) &= 1 - 1 = 0
\end{align*}
\]

None of the fragments identified as the cause

Prediction without fragment

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Why does the model predict class x?

FEATURE COMBINATIONS
NETWORKS
The goal

- We want to be able to identify why any model predicts the given class in a binary classification problem.
  - Not specific to any particular learning algorithm

- We want this to be meaningful in the context of chemical structures
Where we are heading...
How do we get there?

Training data → Model → Predicted network → Assessed network → Prediction: +  
Confidence: 0.8

Query → Feature network
Endpoint definition

1) Activity is caused by the presence of a feature (structural or physicochemical)

2) Inactivity can be described by either:
   1) The lack of an activating feature
   2) The deactivation of all activating features
Descriptor choice

- Descriptors must be represented as a binary fingerprint
- Continuous values (such as logKp) are incorporated through the use of a discretisation algorithm

<table>
<thead>
<tr>
<th>Continuous variable</th>
<th>Discretisation</th>
<th>Discretised variable</th>
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<tr>
<td>0.0</td>
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<td>(-inf, 1.0]</td>
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<td>5.0</td>
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<th>Discretised fingerprint</th>
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Features

- Like with the approaches discussed earlier an entity is removed and a prediction is made on the altered descriptor set.
- In this approach combinations of the bits in the fingerprint are generated.
- A feature contains:
  - Identifier
  - Descriptor subset
  - Fragment
  - Atom list
  - Bond list

When using fragment features
Feature organisation

- Features are organised into hierarchies.
- A parent represents the union of its children.
- The root node represents the feature describing the full query.
- The leaf nodes represent the smallest features.
Fragment networks

- We can use a fragmentation algorithm to map between a structural fingerprint and a set of atom and bonds.
- The fragment can be organised based on the atoms and bonds they represent on the query.
- We can generate the descriptors from the fragments.

<table>
<thead>
<tr>
<th>Fragments</th>
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Fragment networks

- Organise based on atoms and bonds
- Original query structure at the top
- Fragments may occur multiple times while varying in atom and bond lists, these are considered to be independent features
Network generation: descriptors and prediction

Training data

Model

Prediction: +
Confidence: 0.8

Feature network

Query
Calculate descriptors

The descriptors are calculated from the fragments.

A work around may be required to handle novel bits to the fragment.

Structural fingerprints where the contributions of specific atoms can be accounted for work best.
A prediction is made for each descriptor vector and associated with the node.

In the above image green is an inactive prediction and red an active prediction.
Network generation: assessment rules

- **Is predicted active?**
  - yes: **Has predicted inactive ascendant?**
    - yes: **Has predicted inactive parent?**
      - yes: deactivated
      - no: negated
    - no: activity identified
  - no: **Has predicted active child?**
    - yes: deactivating
    - no: ignore

- **Has assessed activating or activity identified child?**
  - yes: activating
  - no: deactivate
Assess the network

Predicted network

Assessed network
Summarise the network

Predicted network

Assessed network
Project the summary

Activating nitrobenzene motif

Aziridine motif deactivated by benzene ring attachment

This structure is **predicted to be active** due to the presence of the nitrobenzene fragment motif
Summaries

• Activity due to an activating feature
• Localised deactivation found

• Activity due to two independent features

• Activity due to a single activating feature
Summaries

- Inactivity due to deactivation of single feature

- Inactivity due to deactivation of single multiple features (multiple deactivating features)

- Inactivity due to lack of an activating feature
Eclipse RCP implementation
Eclipse RCP implementation
Eclipse RCP implementation
Eclipse RCP implementation
KNIME implementation

Model building

Network generation

Prediction

Interpretation
Similarity maps approach – KNIME implementation
Models

• Mutagenicity
  • Curated Hansen dataset
  • Split into train – test – validation
  • Examples shown from validation set
  • SVM, RF, DT, kNN models evaluated
  • Hashed fingerprint model shown

• Skin irritation
  • PaDEL GHS hazard codes
  • Highly biased dataset, utilised class weights and learning performed with Weka
  • DT, kNN and RF models evaluated
  • Hashed fingerprint + logKp binary cut-off
Mutagenicity 1

Similarity maps

Feature networks

Alert 027: Alkylation agent

Alert 329: Aromatic nitro compound

Derek Nexus
Mutagenicity 2

Similarity maps

Feature networks

Alert 027: Alkylating agent

Derek Nexus
Skin irritation examples

Combination features

Fragment features (functional group)

Fragment features (aromatic)

Fragment features (saturated and unsaturated hydrocarbons)
KNOWLEDGE MINING
Knowledge mining

• The developed algorithm provides the interpretation in such a way that it easily lends itself to use for knowledge mining.

(1) Generate folds and iterate through

(2) Model generation for given fold

(3) Prediction and interpretation loop for given fold test structures

(4) Record features and meta-inf
Use cases

• Support the development of human expert knowledge
• Support the development of expert system knowledge base
  • Improve existing alerts
  • Identify new potential toxicophores
SAR pattern network

- The dictionary can be represented as a tree
- The tree represents the relationship between features across the whole dataset
SAR patterns
SAR patterns
Mutagenic example: epoxide
Mutagenic example: quinoline
Mutagenic features

- Nitrofuran motif
- Anthracene motif
- Nitrobenzene motif
- Phenanthrene motif
- Nitrothiophene motif
- Epoxide motif
- N-nitroso motif
- Chloro-alkyl motif
- Bromo-alkyl motif
Summary

• Human expertise is required to abstract the information into a structural alert

Features similar to the N-Nitroso Derek Nexus alert

There is scope for comparing against existing alerts
CONCLUSION
Interpretation: solved or unsolved?

- Multiple interpretation algorithms exist
  - Different levels of granularity
- For some endpoints the feature networks algorithm can remove the accuracy vs interpretation trade-off
- Providing an interpretation can have negative consequences on the trust in the model
  - Right for the wrong reason: potentially rejected model
    - But this may help assess the quality of a model
  - Trend identified differs to experience: potentially rejected model
Knowledge mining

• It is useful to perform knowledge mining activities with more than one approach
  • Variation in cause
  • Variation in support set

• The method has been able to identify existing knowledge and identify potential new structural alerts for:
  • Mutagenicity
  • Skin sensitisation
  • Skin irritation
Feature combination networks for the interpretation of statistical machine learning models: application to Ames mutagenicity

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Thank you
Simple example

- Given the fingerprint \{1,3,4\} we enumerate all combinations of set bits without repetition.
- We can organise into hierarchies based on subset-superset relationships.

\[
C(n, r) = nC_k = nC_k = \frac{n!}{k!(n-k)!}
\]
Limitations of direct enumeration

• Direct enumeration of the fingerprint has limitations
  •Disconnected features (may be undesirable)
  •Must use key based fingerprints to allow for mapping back to the structure
  •Combinatorial explosion
Network generation: process through model

For each node:
1) Generate descriptors
2) Process through model
3) Assign a prediction to the node
Network generation: process through model

We don’t need the information on the network at this point.

Start point is arbitrary.

![Diagram of network generation process]

```
addPrediction()
getFingerprint()
generatePrediction()
```
Network generation: process through model

Network diagram:
- Node 1
- Node 2
- Node 3
- Node 4
- Node 5
- Node 6

Code:
```python
getFingerprint()
addPrediction()
inactive - 0.6
getPrediction()
```
Network generation: process through model

getFingerprint() → getPrediction() ← active – 0.75 ← addPrediction()
Network generation: process through model

Now we start the combination nodes

getFingerprint() → active - 0.95 → getPrediction()

addPrediction() → getFingerprint() → combination nodes
Network generation: process through model

getFingerprint() → addPrediction() → active = 0.72 → getPrediction()
Network generation: process through model

Prediction for the full query structure
Assessment

Start at the root node
Assessment

Start at the root node
Assessment

The nodes' children haven't been assessed
Assessment

Assess child node
The nodes children haven’t been assessed
The node is predicted active and the activity remains in the ascendant nodes

**ACTIVATING**
A child node still remains to be assessed
Assessment

This node is predicted to be inactive and has no children.

**IGNORE**

Assess node
Assessment

This node is predicted to be active, all ascendants are active but it has an ACTIVATING descendant.

ACTIVITY IDENTIFIED

Assess node
We still have a child node to assess.
Assessment

We still have a child node to assess
Assessment

The node is predicted active and the activity remains in the ascendant nodes

**ACTIVATING**

Assess node
Assessment

This node is predicted to be active, all ascendants are active but it has an ACTIVATING descendant.

ACTIVITY_IDENTIFIED

Assess node
Assessment

This node is predicted to be active, it has no ascendants but it has multiple ACTIVATING descendants.

ACTIVITY_IDENTIFIED

Assess node