QSAR modeling

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Modeling of compounds properties

Activity = \( F(\text{structure}) \)

\[
\begin{array}{cccccccc}
D_1 & D_2 & D_3 & D_4 & D_5 & D_6 & \cdots & D_N \\
1 & 0 & 9 & 0 & 11 & 1 & \cdots & 1 \\
4 & 0 & 1 & 0 & 0 & 0 & \cdots & 1 \\
0 & 0 & 0 & 0 & 0 & 4 & \cdots & 6 \\
0 & 2 & 3 & 6 & 0 & 0 & \cdots & 3 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\
4 & 0 & 0 & 0 & 1 & 2 & \cdots & 1 \\
\end{array}
\]

Activity = \( M(E(\text{structure})) \)

\( M \) – mapping function
\( E \) – encoding function
QSAR modeling workflow

Structure

Descriptors (features)

Model

Encoding (represent structure with numerical features)

Mapping (machine learning)
Overall QSAR workflow

OECD principles for the validation, for regulatory purposes, of (Q)SAR models

1) a defined endpoint
2) an unambiguous algorithm
3) a defined domain of applicability
4) appropriate measures of goodness-of-fit, robustness and predictivity
5) a mechanistic interpretation, if possible
Step 1. Data collection

Scientific literature and patents
Databases (ChEMBL, PubChem, BindingDB, etc)

Traditionally modeled compounds should have the same mechanism of action, however using of complex non-linear machine learning method allows to model data sets with mixed or even unknown mechanism of action with reasonable accuracy.

Conditions may substantially influence the results of bioassays (change in temperature, activators, detectors, etc)

Units checking
Step 2. Data curation (normalization)

GRid-INdependent Descriptors (GRIND): A Novel Class of Alignment-Independent Three-Dimensional Molecular Descriptors

Manuel Pastor,† Gabriele Cruciani,*,† Iain McLay,§ Stephen Pickett,§ and Sergio Clementi†

Laboratory on Chemometrics, Department of Chemistry, University of Perugia, Via Elce di Sotto 10, 06123 Perugia, Italy, and CADD Department, Rhone-Poulenc Rorer, Dagenham, Essex RM10 7XS, U.K.

Table 2. Series of 10 Glucose Analogue Inhibitors of Glycogen Phosphorylase

<table>
<thead>
<tr>
<th>no.</th>
<th>$R_\alpha$</th>
<th>$R_\beta$</th>
<th>$pK_a$ (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>H</td>
<td>2.77</td>
</tr>
<tr>
<td>2</td>
<td>C(=O)NH$_2$</td>
<td>H</td>
<td>3.43</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>C(=O)NH$_2$</td>
<td>3.36</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>COOCH$_3$</td>
<td>2.55</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>CH$_2$CN</td>
<td>2.05</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>NH$_2$(-O)NH$_2$</td>
<td>3.85</td>
</tr>
<tr>
<td>7</td>
<td>C(=O)NH$_2$</td>
<td>NHCOOCH$_3$</td>
<td>4.80</td>
</tr>
</tbody>
</table>

strange units
Step 2. Data curation (normalization)

Data from NCI60

- S is charged
- overall charge is +2
- unusual valence of S

Overall charge is +2
HClO4 is represented with separated charges
Nitrogens are covalently bond to Zn?
Wrong stoichiometry?
Step 2. Data curation (normalization)

Removal of mixtures, inorganics, metalorganics, etc

Strip of salts, counterions, etc

Ionization, if necessary (at the particular pH level)

Chemotype normalization, resonance structure and tautomers

Duplicates removal

Manual checking
Step 3. Descriptors: classification

Object type:
- molecular descriptors (single molecules)
- descriptors of molecular ensemble (mixtures, materials)
- reaction descriptors (reactions)

Descriptor origin:
- calculated from the structure
- empirical (Hammet constants, lipophilicity chemical shifts in NMR, etc)

Locality:
- local (atom charge)
- global (molecular weight, molecular volume, lipophilicity, etc)

Dimensionality:
- 1D (number of methyl groups, molecular weight, etc)
- 2D (topological indices, fragmental descriptors)
- 3D (molecular volume, quantum chemical descriptors)
- 4D (based on a set of conformers)

Calculation method:
- physico-chemical (lipophilicity, etc)
- topological (invariants of molecular graph, Randic index, Wiener index, etc)
- fragmental (fingerprints, etc)
- pharmacophore
- spatial (moment of inertia, etc)
- quantum-chemical (energy of HOMO/LUMO, etc)

etc. 

R. Todeschini and V. Consonni Handbook of Molecular Descriptors, 2008
Atom-centric (augmented atoms) fingerprints

Generate substructures starting from each atom and considering all its neighbors up to the specified distance (radius or diameter).

Morgan fingerprints, Extended-connectivity fingerprints (ECFP). Functional-class fingerprints (FCFP), etc.

radius=2 (diameter=4)

Atom-centric (augmented atoms) fingerprints

Morgan fingerprints
radius=2
(diameter=4)

Morgan fingerprints
radius=4
(diameter=8)

identical fingerprints

different fingerprints
Fingerprints

Each molecule has variable length set of substructures – variable length fingerprints

2-bond sequences

<table>
<thead>
<tr>
<th></th>
<th>N–C–C</th>
<th>C–C–O</th>
<th>C–C=O</th>
<th>C–C–C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Compound 2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Hashed fingerprints

Have fixed length (usually 512, 1024 or 2048 bits)

Each substructure activates several bits (usually 4-5) to avoid collisions and produce bit string of enough density

Missing bits mean that certain substructures are not presented, Active bits mean that certain substructure may be present (but due to possible collisions one cannot be sure)
Folding of fingerprints and keys bit strings

To increase density of very sparse bit vectors

\[
\begin{array}{c}
\text{H}_2\text{N}-
\end{array}
\]

\[
\begin{array}{c}
\text{OH}
\end{array}
\]

\[
\begin{array}{c}
0 & 0 & 0 & 1 & 0 & 0 & 1 & 1 & 0 & 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 1
\end{array}
\]

n bit fingerprints

\[
\begin{array}{c}
0 & 0 & 0 & 1 & 0 & 0 & 1 & 1 & 0 & 1
\end{array}
\]

n/2 bits

\[
\begin{array}{c}
0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 1
\end{array}
\]

OR

\[
\begin{array}{c}
0 & 0 & 1 & 1 & 1 & 0 & 1 & 1 & 1 & 1
\end{array}
\]

n/2 bit fingerprint

Usually optimal density is 0.2-0.3
Step 4. Feature processing

Feature transformations:
linear and non-linear scaling

\[ z_i = \frac{x_i - \bar{x}}{sd} \quad sd = \sqrt{\frac{n}{n-1} \sum_{i=1}^{n} (x_i - \bar{x})^2} \]

\[ z_i = \frac{1}{1 + e^{-x_i}} \quad \text{range (0; 1)} \]

\[ z_i = x_i^2 \quad \text{add quadratic term} \]

Feature combinations:

\[ z_{ij} = x_i x_j \]

Feature selection:
removal of correlated descriptors (important e.g. for linear regression models)
removal of descriptors with missing values
removal constant and near constant features
removal of descriptors with low correlation with the target property
step-wise feature selection
evolutionary feature selection (genetic algorithm, etc)
## Step 5. Model building

### Unsupervised clustering

![Unsupervised clustering](image)

### Supervised

<table>
<thead>
<tr>
<th>Regression</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple linear regression (MLR)</td>
<td>Logistic regression</td>
</tr>
<tr>
<td>Partial linear regression (PLS)</td>
<td>Naïve Bayes (NB)</td>
</tr>
<tr>
<td>Gaussian Process (GP)</td>
<td></td>
</tr>
<tr>
<td>Decision trees (DT)</td>
<td></td>
</tr>
<tr>
<td>Support vector machine (SVM)</td>
<td></td>
</tr>
<tr>
<td>Neural nets (NN)</td>
<td></td>
</tr>
<tr>
<td>Random forest (RF)</td>
<td></td>
</tr>
<tr>
<td>k-Nearest neighbors (kNN)</td>
<td></td>
</tr>
</tbody>
</table>
Hansch equation

\[ \frac{1}{C} = 4.08\pi - 2.14\pi^2 + 2.78\sigma + 3.38 \]

\( \pi = \log P_X - \log P_H \)

\( \sigma \) - Hammet constant

Plant growth inhibition activity of phenoxyacetic acids

Free-Wilson models

Inhibition activity of compounds against *Staphylococcus aureus*

\[ \text{Act} = 75R_H - 112R_{CH_3} + 84X_{Cl} - 16X_{Br} - 26X_{NO_2} + 123Y_{NH_2} + 18Y_{NHC(=O)CH_3} - 218Y_{NO_2} \]
Simulated data set of actives and inactives with two descriptors – MW and logP
IF $\log P \geq 3.2$ AND $\text{MW} \geq 255$ THEN compound is NO

IF $\log P < 3.2$ AND $\text{MW} < 358$ THEN compound is NO

IF $\text{MW} < 255$ THEN compound is YES
Decision tree
Random Forest

Initial dataset

Bootstrap sample

Bootstrap sample

Bootstrap sample

Random feature subspace in each node

CART tree_1

CART tree_2

CART tree_3

Combined prediction
Consensus (ensemble) modeling

Models should be not correlated
(one may use different combination of descriptors and machine learning methods)
Consensus (ensemble) modeling
**Step 6. Validation**

### Test set (usually 20-25% of the work set)

<table>
<thead>
<tr>
<th>working set</th>
<th>1.2</th>
<th>1.3</th>
<th>1.7</th>
<th>2.0</th>
<th>2.2</th>
<th>2.8</th>
<th>3.1</th>
<th>3.2</th>
<th>3.2</th>
<th>3.6</th>
<th>4.7</th>
<th>5.7</th>
<th>5.8</th>
<th>6.4</th>
<th>7.2</th>
<th>8.1</th>
<th>9.0</th>
<th>9.1</th>
<th>9.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>random test set</td>
<td>1.2</td>
<td>1.3</td>
<td>1.7</td>
<td>2.0</td>
<td>2.2</td>
<td>2.8</td>
<td>3.1</td>
<td>3.2</td>
<td>3.2</td>
<td>3.6</td>
<td>4.7</td>
<td>5.7</td>
<td>5.8</td>
<td>6.4</td>
<td>7.2</td>
<td>8.1</td>
<td>9.0</td>
<td>9.1</td>
<td>9.2</td>
</tr>
<tr>
<td>stratified test set</td>
<td>1.2</td>
<td>1.3</td>
<td>1.7</td>
<td>2.0</td>
<td>2.2</td>
<td>2.8</td>
<td>3.1</td>
<td>3.2</td>
<td>3.2</td>
<td>3.6</td>
<td>4.7</td>
<td>5.7</td>
<td>5.8</td>
<td>6.4</td>
<td>7.2</td>
<td>8.1</td>
<td>9.0</td>
<td>9.1</td>
<td>9.2</td>
</tr>
</tbody>
</table>

### Cross-validation

<table>
<thead>
<tr>
<th>working set</th>
<th>1.2</th>
<th>1.3</th>
<th>1.7</th>
<th>2.0</th>
<th>2.2</th>
<th>2.8</th>
<th>3.1</th>
<th>3.2</th>
<th>3.2</th>
<th>3.6</th>
<th>4.7</th>
<th>5.7</th>
<th>5.8</th>
<th>6.4</th>
<th>7.2</th>
<th>8.1</th>
<th>9.0</th>
<th>9.1</th>
<th>9.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>fold 1</td>
<td>1.2</td>
<td>1.3</td>
<td>1.7</td>
<td>2.0</td>
<td>2.2</td>
<td>2.8</td>
<td>3.1</td>
<td>3.2</td>
<td>3.2</td>
<td>3.6</td>
<td>4.7</td>
<td>5.7</td>
<td>5.8</td>
<td>6.4</td>
<td>7.2</td>
<td>8.1</td>
<td>9.0</td>
<td>9.1</td>
<td>9.2</td>
</tr>
<tr>
<td>fold 2</td>
<td>1.2</td>
<td>1.3</td>
<td>1.7</td>
<td>2.0</td>
<td>2.2</td>
<td>2.8</td>
<td>3.1</td>
<td>3.2</td>
<td>3.2</td>
<td>3.6</td>
<td>4.7</td>
<td>5.7</td>
<td>5.8</td>
<td>6.4</td>
<td>7.2</td>
<td>8.1</td>
<td>9.0</td>
<td>9.1</td>
<td>9.2</td>
</tr>
<tr>
<td>fold 3</td>
<td>1.2</td>
<td>1.3</td>
<td>1.7</td>
<td>2.0</td>
<td>2.2</td>
<td>2.8</td>
<td>3.1</td>
<td>3.2</td>
<td>3.2</td>
<td>3.6</td>
<td>4.7</td>
<td>5.7</td>
<td>5.8</td>
<td>6.4</td>
<td>7.2</td>
<td>8.1</td>
<td>9.0</td>
<td>9.1</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Predictions of different folds are combined to calculate the final predictive measure.
### Step 6. Measures of predictive ability of models

#### Classification

<table>
<thead>
<tr>
<th>Measure</th>
<th>Formula</th>
<th>Validity range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>( \frac{TP + TN}{N} )</td>
<td>[0; 1]</td>
</tr>
<tr>
<td>Specificity</td>
<td>( \frac{TN}{TN + FP} )</td>
<td>[0; 1]</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>( \frac{TP}{TP + FN} )</td>
<td>[0; 1]</td>
</tr>
<tr>
<td>Balanced accuracy</td>
<td>( \frac{\text{Specificity} + \text{Sensitivity}}{2} )</td>
<td>[0; 1]</td>
</tr>
<tr>
<td>Kappa</td>
<td>( \frac{\text{accuracy} - \text{baseline}}{1 - \text{baseline}} )</td>
<td>[0; 1]</td>
</tr>
</tbody>
</table>

#### Confusion matrix

<table>
<thead>
<tr>
<th>Predicated positive class (1)</th>
<th>Predicated negative class (0)</th>
<th>Observed positive class (1)</th>
<th>Observed negative class (0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>true positive (TP)</td>
<td>false negative (FN)</td>
<td>true positive (TP)</td>
<td>false negative (FN)</td>
</tr>
<tr>
<td>false positive (FP)</td>
<td>true negative (TN)</td>
<td>false positive (FP)</td>
<td>true negative (TN)</td>
</tr>
</tbody>
</table>

#### Balanced accuracy Calculation

\[
\text{baseline} = \frac{(TN + FP)(TN + FN) + (TP + FN)(TP + FP)}{N^2}
\]

#### Kappa Calculation

\[
\text{Kappa} = \frac{\text{accuracy} - \text{baseline}}{1 - \text{baseline}}
\]

#### Matthews correlation coefficient (MCC)

\[
\text{MCC} = \frac{TP \times TN + FP \times FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}}
\]

\[
\text{MCC} \in [-1; 1]
\]
Regression

Determination coefficient

\[ Q^2 = 1 - \frac{\sum (y_{i,\text{pred}} - y_{i,\text{obs}})^2}{\sum (y_{i,\text{pred}} - y_{\text{obs}})^2} \]

Root mean squared error

\[ \text{RMSE} = \sqrt{\frac{\sum (y_{i,\text{pred}} - y_{i,\text{obs}})^2}{N - 1}} \]

Mean absolute error

\[ \text{MAE} = \frac{1}{N} \sum_{i=1}^{N} |y_{i,\text{pred}} - y_{i,\text{obs}}| \]
Step 7. Applicability domain (AD)

Extrapolation to very distant objects is dangerous

There is a need to define the domain where our model is reliable (models are not universal!)

Only compounds which are similar to the training set compounds should be included in applicability domain of the model. One should estimate similarity of new compounds (test set, etc) to the training set compounds.
Step 7. Applicability domain (AD) measures

**Bounding box** - based on descriptor range

- internal regions are usually empty, especially if the number of descriptors is big
- it doesn’t take into account descriptor correlation

**Distance** from training set compounds *in descriptor space*

**Distance** from training set compounds *in model space*

Requires several models (e.g. consensus model, bootstrap models)

One-class SVM

Conformal predictions
Step 7. Applicability domain (AD) example
Step 8. Interpretation of QSAR models

Why interpretation is important?

Found active/inactive patterns which can be used for optimization of compound properties

Retrieve trends of stricture-activity relationships which can be used for knowledge-base model validation

Regulatory purposes
Step 8. Interpretation of QSAR models

Principles and issues

Model should be predictive

Interpretation is valid within the applicability domain of the model

Interpretation results are data set dependent
Step 8. Interpretation of QSAR models

plant growth inhibition activity of phenoxyacetic acids

\[ \frac{1}{C} = 4.08\pi - 2.14\pi^2 + 2.78\sigma + 3.38 \]

rate of penetration of membranes in the plant cell

\[ \pi = \log P_X - \log P_H \]

\[ \sigma \text{ - Hammet constant} \]

Hansch equation

Free-Wilson models

Inhibition activity of compounds against *Staphylococcus aureus*

R is H or CH\(_3\);

X is Br, Cl, NO\(_2\) and

Y is NO\(_2\), NH\(_2\), NHC(=O)CH\(_3\)

\[ \text{Act} = 75R_H - 112R_{CH_3} + 84X_{Cl} - 16X_{Br} - 26X_{NO2} + 123Y_{NH2} + 18Y_{NHC(=O)CH_3} - 218Y_{NO2} \]
Step 8. Interpretation of QSAR models

347 agonists of $5$-HT$_{1A}$ receptor

- Ar: substituted (hetero)aryls
- L: polymethylene chain
- R: various (poly)cyclic residues

<table>
<thead>
<tr>
<th>Ar</th>
<th>OMe</th>
<th>Cl</th>
<th>Cl</th>
<th>CF$_3$</th>
<th>N</th>
<th>O$_2$N</th>
<th>Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLS</td>
<td>0.84</td>
<td>0.18</td>
<td>0.03</td>
<td>-0.04</td>
<td>-0.06</td>
<td>-0.09</td>
<td>-0.11</td>
</tr>
<tr>
<td>RF</td>
<td>0.27</td>
<td>0.24</td>
<td>0.04</td>
<td>0.07</td>
<td>-0.02</td>
<td>0.11</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>L</th>
<th>-(CH$_2$)$_6$</th>
<th>-(CH$_2$)$_5$</th>
<th>-(CH$_2$)$_4$</th>
<th>-(CH$_2$)$_3$</th>
<th>-(CH$_2$)$_2$</th>
<th>-CH$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLS</td>
<td>0.8</td>
<td>0.71</td>
<td>0.81</td>
<td>0.08</td>
<td>-0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>RF</td>
<td>0.14</td>
<td>0.19</td>
<td>0.14</td>
<td>-0.01</td>
<td>-0.03</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Step 8. Interpretation of QSAR models

Partial derivatives is used to calculate contributions of single features. It is applicable to any model built on meaningful (interpretable) descriptors. May be calculated analytically or numerically.

\[
C = f(x + \delta) - f(x) \quad \text{forward difference}
\]

\[
C = f(x) - f(x - \delta) \quad \text{backward difference}
\]

\[
C = \frac{f(x + \delta) - f(x - \delta)}{2\delta} \quad \text{central difference}
\]

Estimated contributions of separate substructural features can be mapped back on the structure to reveal contribution of fragments.

\[
\begin{align*}
\text{C–C–N} & \quad -3 \\
\text{C–C–O} & \quad +6
\end{align*}
\]
Step 8. Interpretation of QSAR models

Universal approach

\[ \text{Activity}_{\text{pred}}(A) = x \]
\[ \text{Activity}_{\text{pred}}(B) = y \]
\[ \text{Contribution}(C) = W(C) = x - y \]

Step 8. Interpretation of QSAR models

<table>
<thead>
<tr>
<th>Descriptors</th>
<th>Algorithm</th>
<th>Balanced Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiRMS</td>
<td>RF</td>
<td>0.817</td>
</tr>
<tr>
<td></td>
<td>SVM</td>
<td>0.800</td>
</tr>
<tr>
<td>Dragon</td>
<td>RF</td>
<td>0.816</td>
</tr>
<tr>
<td></td>
<td>SVM</td>
<td>0.793</td>
</tr>
</tbody>
</table>

Step 8. Interpretation of QSAR models

Acute oral toxicity on rats

Step 8. Interpretation of QSAR models

Toxicity towards Tetrahymena pyriformis

Chlorine

Bromine

Iodine

Aliphatic halogens (F < Cl < Br < I)

unpublished results
<table>
<thead>
<tr>
<th>Case number</th>
<th>Do specific interactions of a ligand with its target exist or important?</th>
<th>Is an orientation of a ligand relatively its target known?</th>
<th>Fragments selection and grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO (e.g. passive diffusion through membranes, solubility, lipophilicity, etc)</td>
<td>not relevant</td>
<td>can be done by the researcher based on his own knowledge</td>
</tr>
<tr>
<td>2</td>
<td>YES (ligand-receptor interactions, host-guest complexes, etc)</td>
<td>YES</td>
<td>consider fragments’ positions relatively to the target and observed or predicted interactions</td>
</tr>
<tr>
<td>3</td>
<td>NO</td>
<td>NO</td>
<td>MMP can be applied, silently assumed that all compounds have the same interaction mode</td>
</tr>
</tbody>
</table>
**Step 8. Interpretation of QSAR models**

**Interpretation of Quantitative Structure–Activity Relationship Models: Past, Present, and Future**

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**Table 7. Applicability of Interpretation Approaches to QSAR Models**

<table>
<thead>
<tr>
<th>Models</th>
<th>Descriptors</th>
<th>non-interpretable</th>
</tr>
</thead>
<tbody>
<tr>
<td>linear regression</td>
<td>regression coefficients (Hansch, Free-Wilson)</td>
<td></td>
</tr>
<tr>
<td>PLS (OPLS, O2PLS, etc)</td>
<td>regression coefficients, X- and Y-scores, variable importance</td>
<td></td>
</tr>
<tr>
<td>decision trees</td>
<td>logical rules</td>
<td></td>
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<tr>
<td>NN</td>
<td>variable importance based on weights and biases, variable contributions</td>
<td>universal structural interpretation, similarity maps, computational matched molecular pairs and series</td>
</tr>
<tr>
<td>RF</td>
<td>variable importance based on permutation, variable contributions</td>
<td></td>
</tr>
<tr>
<td>NN, SVM, RF</td>
<td>rule extraction</td>
<td></td>
</tr>
<tr>
<td>any model including consensus ones</td>
<td>partial derivatives, variable importance based on permutation, sensitivity analysis</td>
<td></td>
</tr>
<tr>
<td>Interpretation paradigm</td>
<td>model → descriptors → (structure) or model → structure</td>
<td>model → structure</td>
</tr>
</tbody>
</table>
Interpretation results of valid predictive models should converge independent of:

- interpretation approach
- descriptors
- machine learning method

All models are interpretable but not all end-points
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**Partial derivatives** is used to calculate contributions of single features. It is applicable to any model built on meaningful (interpretable) descriptors. May be calculated analytically or numerically.

\[
C = f(x + \delta) - f(x) \\
C = f(x) - f(x - \delta) \\
C = \frac{f(x + \delta) - f(x - \delta)}{2\delta}
\]

- forward difference
- backward difference
- central difference

Estimated contributions of separate substructural features can be mapped back on the structure to reveal contribution of fragments.