Modelling the *in vitro* cytotoxicity of metal/metal oxide and silica nanomaterials under diverse experimental conditions

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Introduction

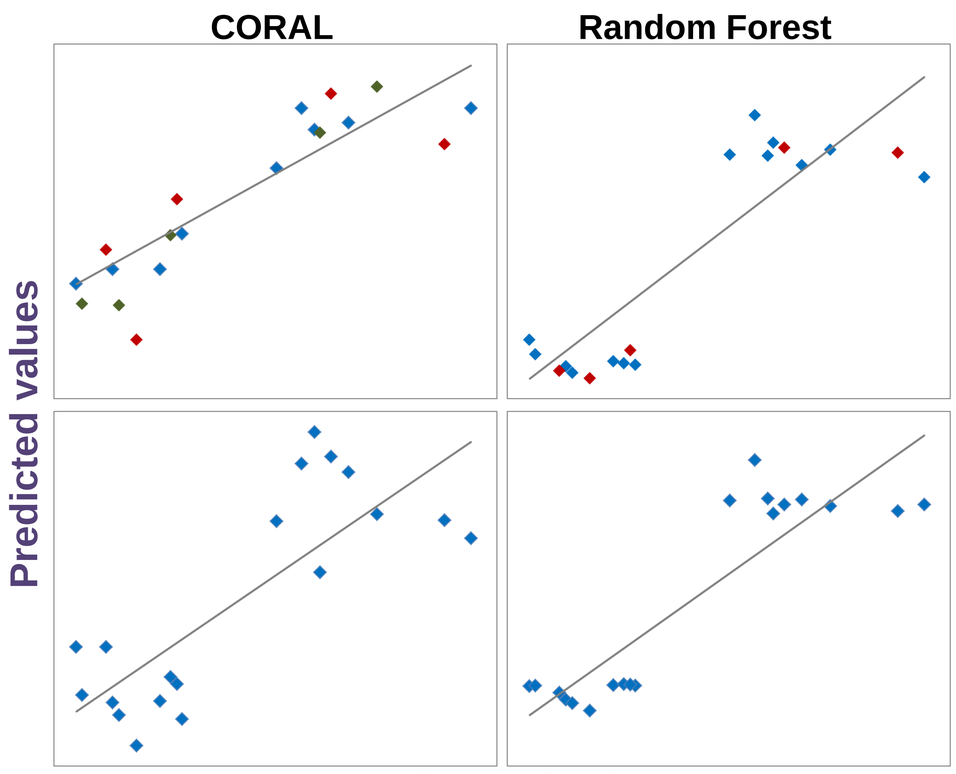
- Nanomaterials are increasingly being used in technological applications.
- However, concerns have been raised regarding their potential toxicity..
- There is considerable interest in using **computational models** to predict toxicity.
- This could enable "**safety-by-design**"
- The MODENA COST action[1] and NanoPUZZLES[2] project support the "**safety-by-design**" paradigm.
- The current work reports preliminary results of modelling **WST-1 *in vitro* cytotoxicity** experimental data for **19 uncoated silica (SiO_2)** nanomaterials kindly provided by the MODENA COST action.
- Modelling was based on the quantitative structure-activity relationship (**nano-QSAR**) approach.

The adopted nano-QSAR paradigm

- In this work, the traditional paradigm of QSAR models for chemical compounds was modified as follows:

Experimental conditions like exposure duration and cell type were used as descriptors together with descriptors derived from nanomaterials' **physicochemical properties** such as size, aspect ratio and zeta potential.

Preliminary results



Subset	CORAL R^2	Random Forest R^2
Training	0.90	0.74
Sub-training	0.86	NA
Calibration	0.98	NA
Test	0.59	0.90

Model	LOO R^2
CORAL	0.64
Random Forest	0.79

References

1. Modelling Nanomaterial Toxicity 'MODENA' COST (http://www.modena-cost.eu/)
2. NanoPUZZLES project (http://www.nanopuzzles.eu) .
3. CORAL software (http://www.insilico.eu/CORAL) .
4. A. Liaw and M. Wiener (2002). Classification and Regression by randomForest. R News 2(3), 18--22.
5. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. (https://www.R-project.org/)

Materials and methods

In the current work, the Monte Carlo method implemented in the CORAL software[3] (version: December 17, 2014) and the Random Forest algorithm implemented in the randomForest[4] R[5] package (version 4.6-12) were compared.

- **The CORAL software uses strings as input e.g. pseudo-SMILES:**

Subset	ID	Pseudo-SMILES	Exp.
+	119	AGHKM	-1.299
-	103	BDHKM	-0.872
#	123	AGHJL	0.365

CORAL (CORrelation And Logic)

- **Subset**: +/-/# stand for sub-training/calibration/test sets.
- **Pseudo-SMILES**: five descriptors derived from experimental conditions and physicochemical properties for the selected nanomaterials were coded according to the following scheme:
  i. Treatment time: 'A' = 24h; 'B' = 48h;
  ii. Cell type: 'C' = 16HBE; 'D' = A549; 'E' = HaCaT; 'F' = NRK-52E; 'G' = THP-1 macrophage;
  iii. Average size: 'H' ≤ 30 nm; 'I' > 30 nm;
  iv. Aspect ratio: 'J' = 1; 'K' > 1;
  v. Zeta potential: 'L' > -33 mV ; 'M' ≤ -33 mV;
- **Exp.**: WST-1 *in vitro* cytotoxicity: -log[EC_{25} (mm^2/ml)]

- **Bit-strings derived from the CORAL pseudo-SMILES were used as input for the R software:**

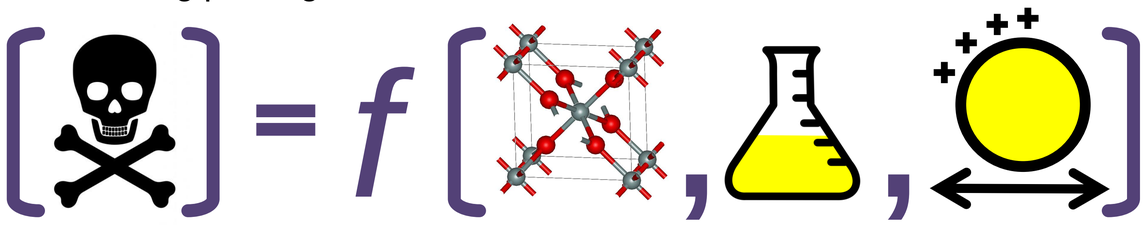
ID	Pseudo-SMILES	A	B	C	D	E	F	G	H	I	J	K	L	M	Exp.
119	AGHKM	1	0	0	0	0	0	1	1	0	0	1	0	1	-1.299
103	BDHKM	0	1	0	1	0	0	0	1	0	0	1	0	1	-0.872
123	AGHJL	1	0	0	0	0	0	1	1	0	1	0	1	0	0.365

Random Forest models were built with the default hyperparameters:
- Ntree (number of trees) = **500**
- Mtry (number of variables considered for each split) = **4**

- **Validation of modelling approaches:**
  1. Training (14 instances) and test (5 instances)
     – CORAL: training = sub-training (9) and calibration (5)
  2. "External" leave-one-out (LOO) cross-validation

Future works

- Optimise the Random Forest model hyperparameters;
- Model nanomaterials with different core/surface chemical composition (e.g. **metal oxides** and **metals**), according to the following paradigm:



- Consider additional experimental conditions such as the serum concentration, the dispersion protocol and assay type;

Acknowledgements

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