Predictions of Intrinsic Aqueous Solubility of Crystalline Drug-like Molecules

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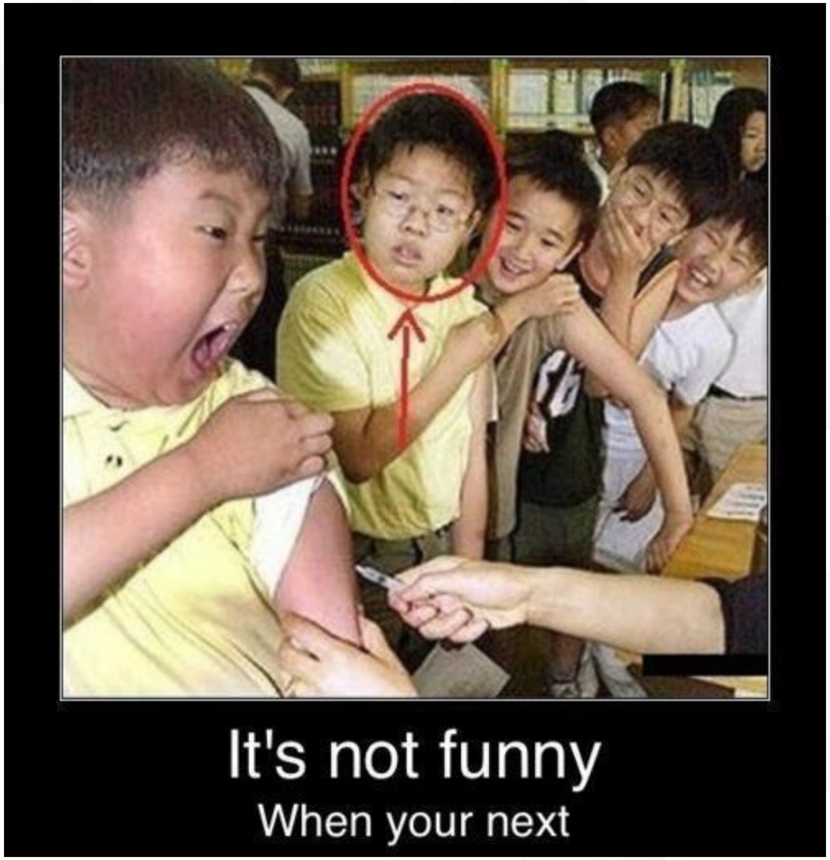
Overview

- **Introduction.**
- **Solution model** – Our solubility prediction model.
- **Results** – The performance of the solubility predictions.
- **Further models** – Work following on from the initial model.
- **Current/future work** – Where we are currently and where we are going.

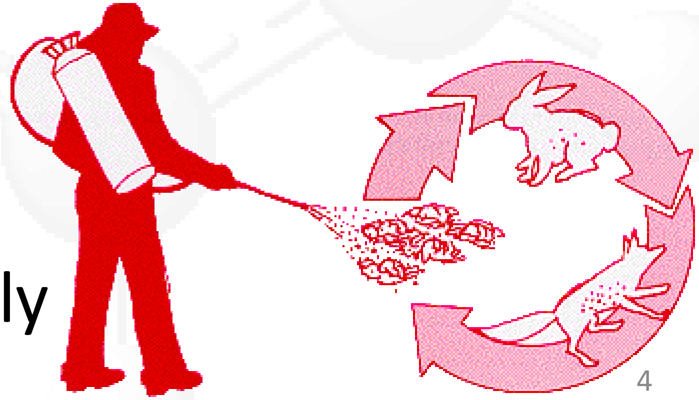
Why is solubility prediction important?

- Crucial factor to control bioavailability of drug candidates.
- Critical component in determining the environmental impact of pesticides.
- Accurate *in silico* predictions of solubility can save time and money.

Why should we care about solubility ?



- New drug candidates are often more insoluble than their predecessors.
- Formulation of these drugs often involve less pleasant administration methods.



- Certain pesticides can cause extensive damage and potentially enter the water cycle.

Existing Theoretical Approaches

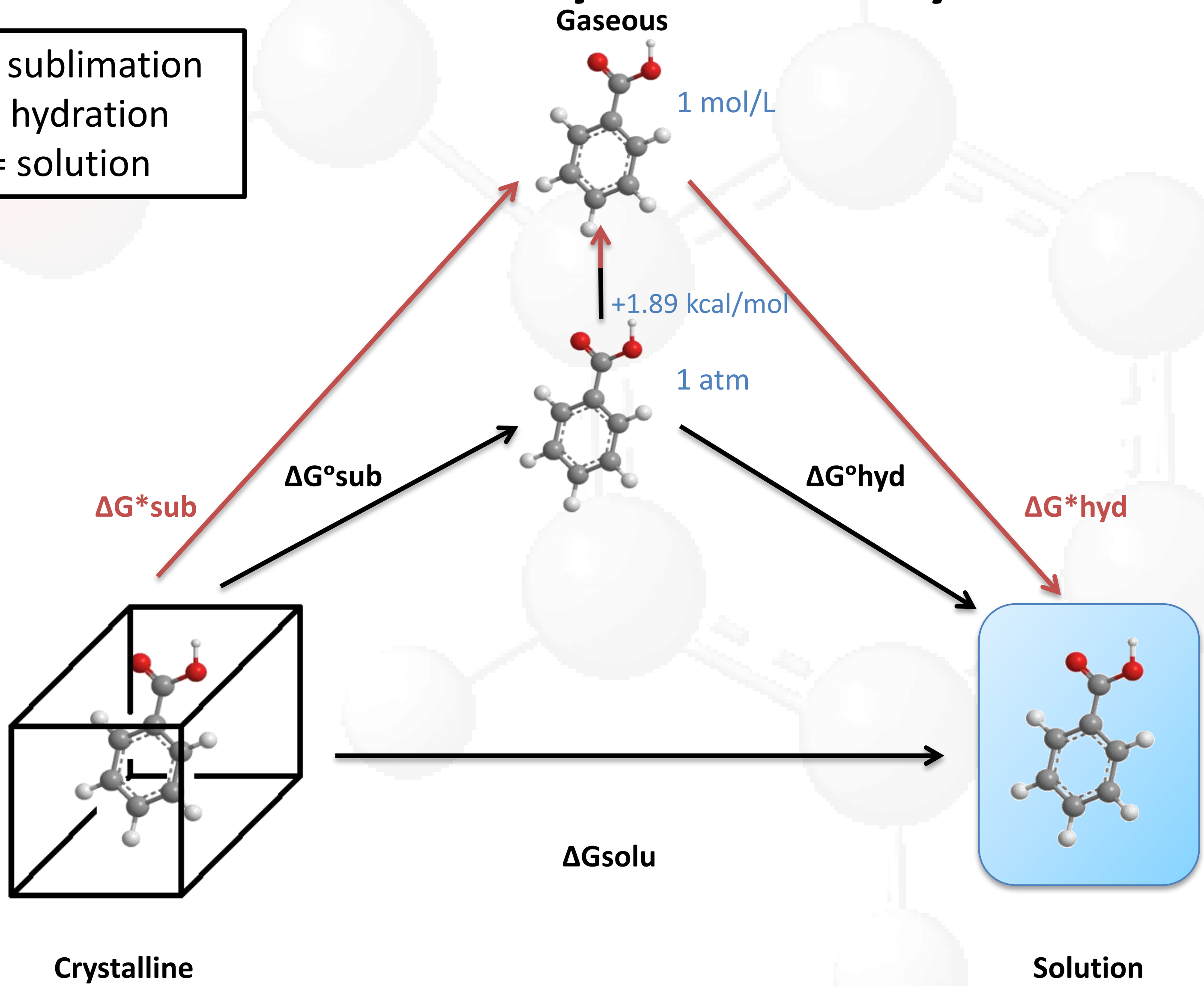
- So far, although theoretical methods have shown promise, they have not matched the accuracy of QSPR. Theoretical methods do have the advantage of being physically tractable.
- Industry also requires high through put methods. QSPR models are generally much faster than computational chemistry models.
- There are many theoretical models to make solubility predictions.

Our Methodologies

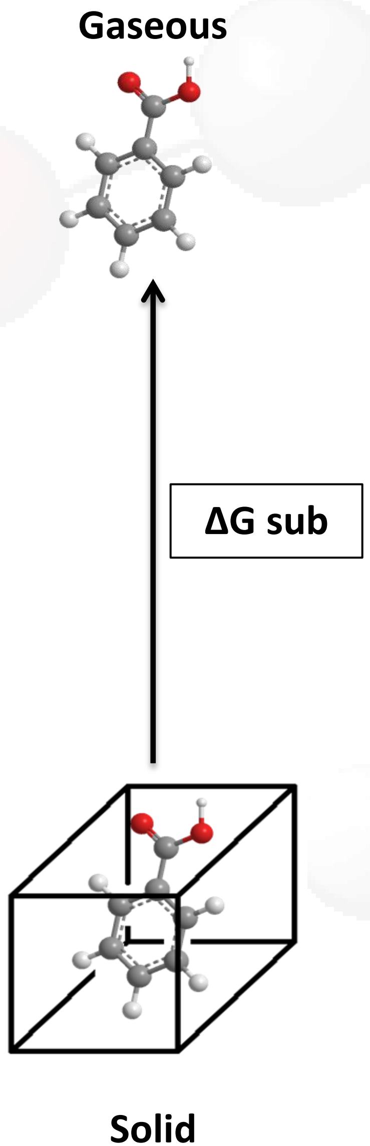
- We have decomposed the solution (solu) free energy prediction in to two distinct steps.
  - Sublimation (sub)
  - Hydration (hyd)
- We have applied a range of methodologies to each step.
- Methodologies include simulation, QM calculation and machine learning.

Thermodynamic cycle

Sub = sublimation
Hyd = hydration
Solu = solution

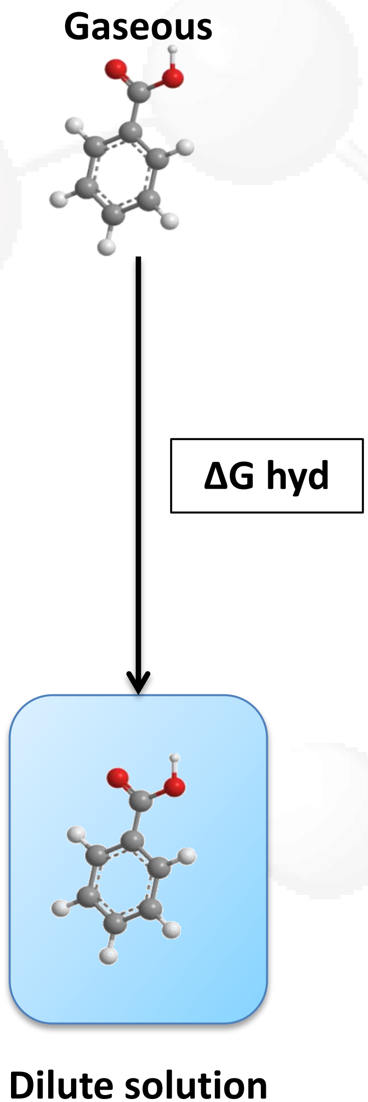


Sublimation : Predictions by DMACRYS



- DMACRYS a periodic lattice simulation program.
- Electrostatics, from distributed multipoles.
- Buckingham potential to account for repulsion and dispersion.
- Calculates lattice energy and crystal entropy from phonon modes.
- Gas phase contributions calculated in Gaussian 09.

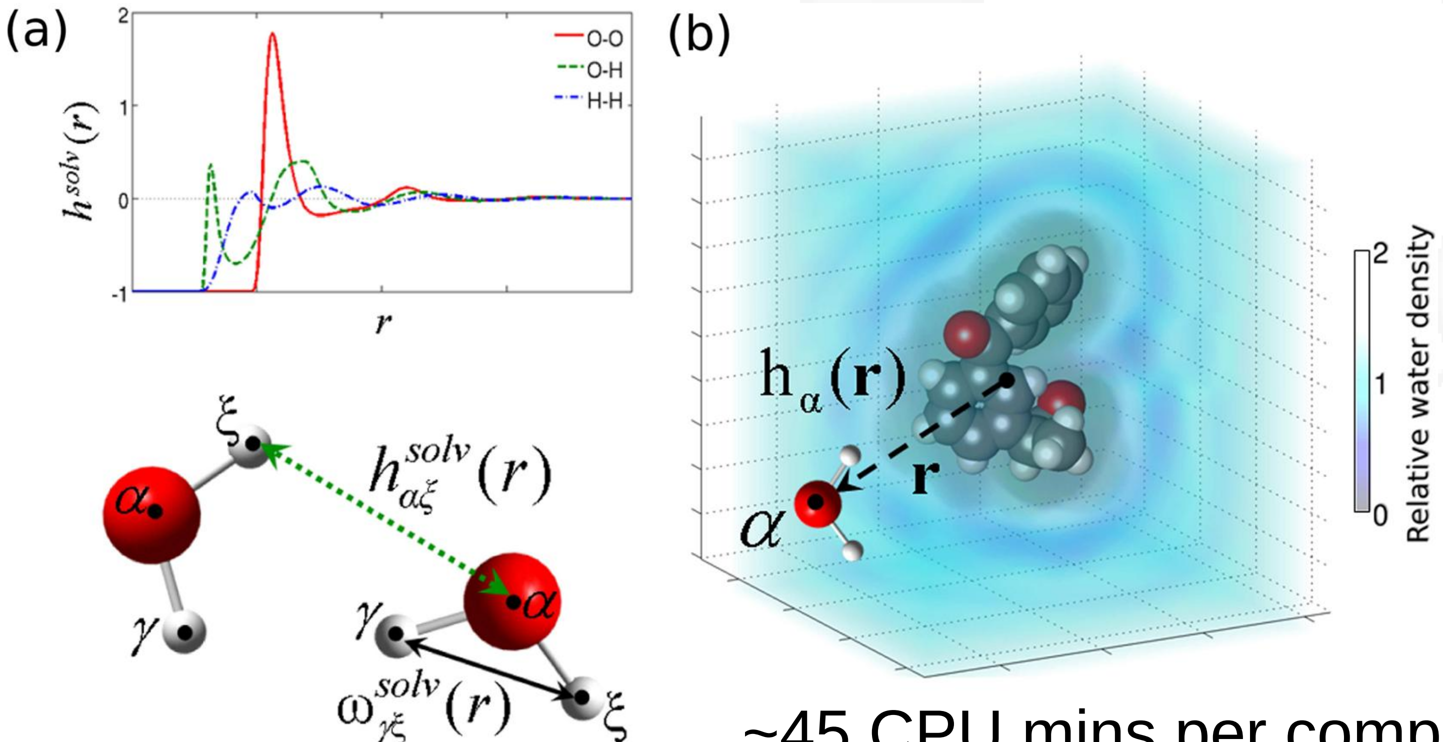
Hydration: Solvation models



- Continuum solvent, solvation model based on density (SMD).
- An integral equation theory (IET) of molecular liquids methodology the Reference Interaction Site Model (RISM).

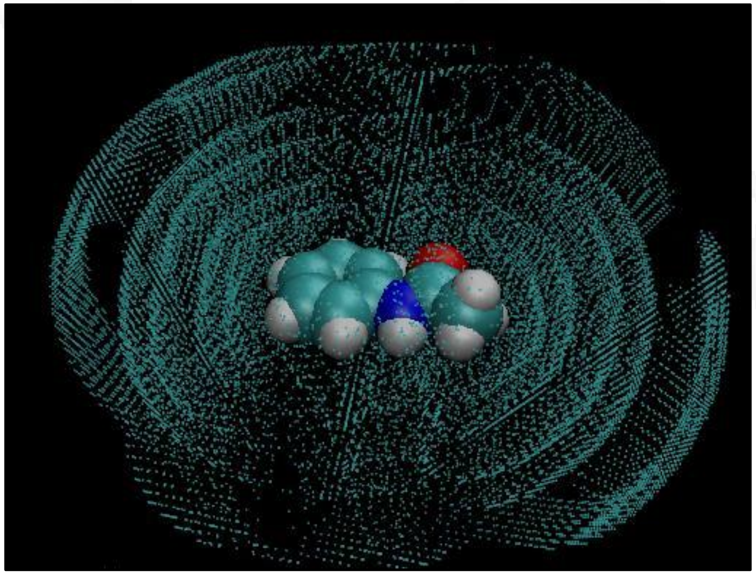
Hydration: RISM

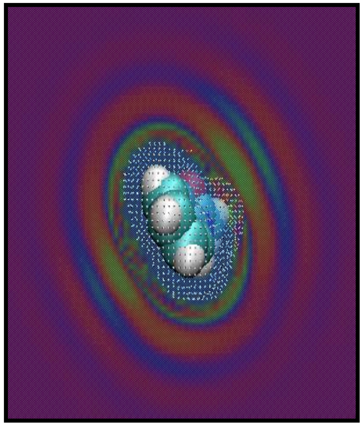
- Combines features of explicit and implicit solvent models.
- Solvent density is modelled, but no explicit molecular coordinates or dynamics.

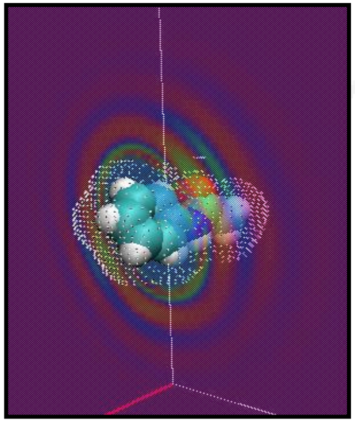


~45 CPU mins per compound

Hydration: RISM







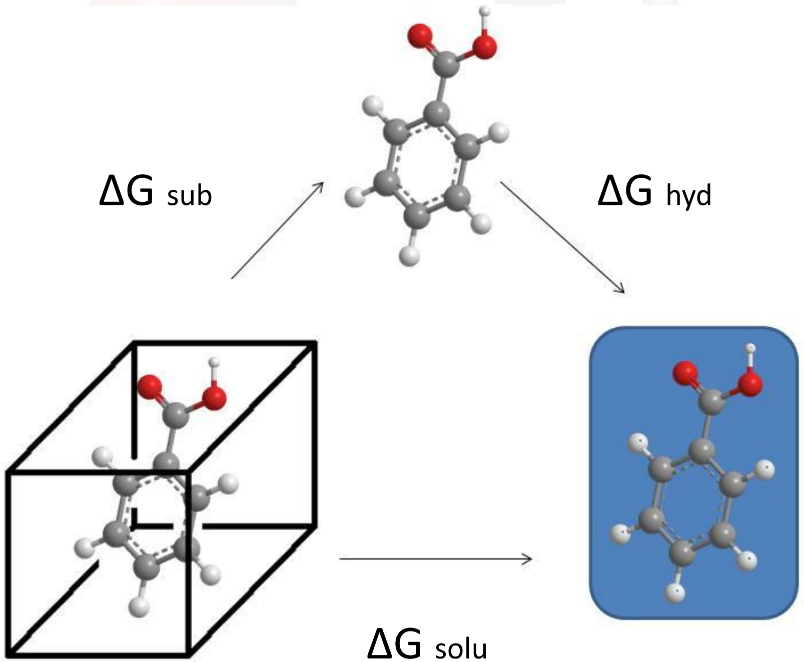
- We use the 3D RISM variation.
- We employ the Kovalenko-Hirata (KH) closure and Gaussian fluctuation free energy functional.
- We also employ the universal correction (UC).

$$\Delta G_{hyd}^{3DRISM-KH/UC} = \Delta G_{hyd}^{3DRISM} + a(\rho V) + b$$

- The methodology we used will be referred to as 3DRISM-KH/UC.

David, S. Palmer., Andrey I Frolov, Ekaterina L Ratkova and Maxim V Fedorov,. *Journal of Physics: Condensed Matter* **2010,** *22* (49), 492101.

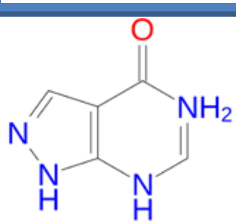
Solution Free Energy

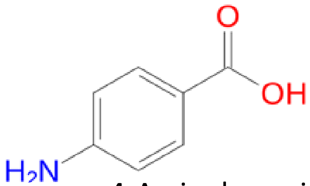


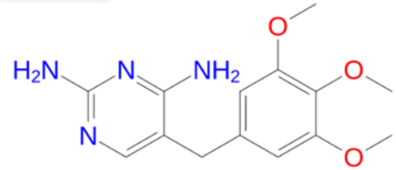
- The sum of our predictions of ΔG_{sub} and ΔG_{hyd} produce a ΔG_{solu} prediction.
- These methods were carried out for 25 chemically diverse drug-like molecules.
- Chemical accuracy ~4 kJ/mol or ~ 1 LogS unit.
- Useful predictions are within the standard deviation (SD) of the experimental values.

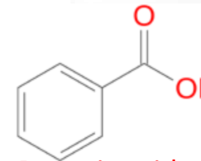
Data set selection

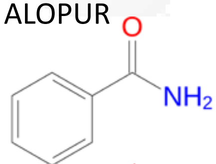
- The thermodynamically most stable polymorph was selected
- 10 had available experimental sublimation and hydration free energies. (in red).

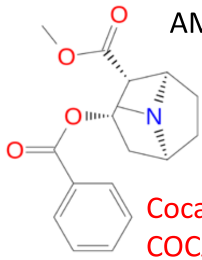

Allopurinol
ALOPUR

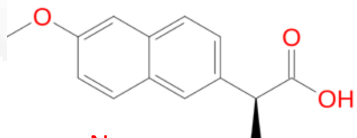

4-Aminobenzoic acid
AMBNAC04

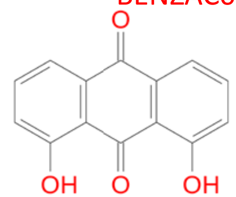

Trimethoprim
AMXBPM10

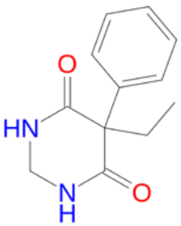

Benzoic acid
BENZAC02

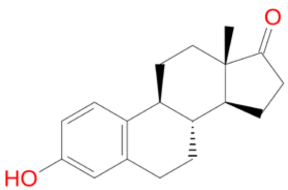

Benzamide
BZAMID02

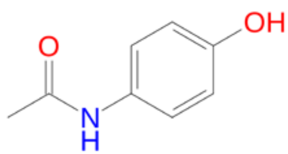

Cocaine
COCAIN10

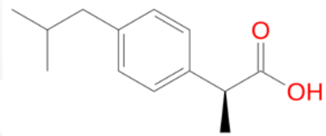

Naproxen
COYRUD11

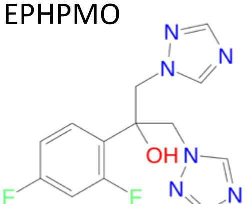

Danthron
DAHNQU06

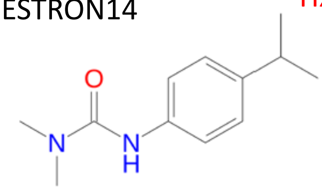

Primidone
EPHPMO

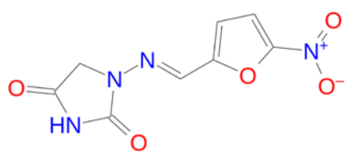

Estrone
ESTRON14

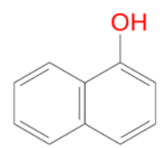

Acetaminophen
HXACAN04

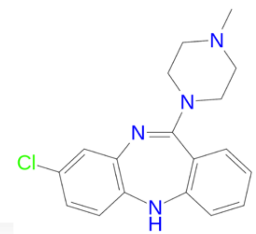

Ibuprofen
IBPRAC01

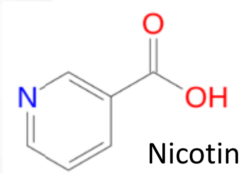

Fluconazole
IVUQOF

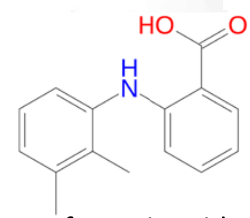

Isoproturon
JODTUR01

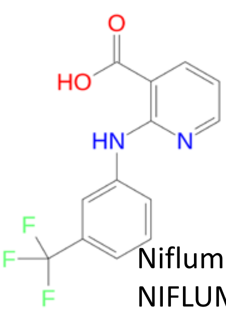

Nitrofurantoin
LABJON01

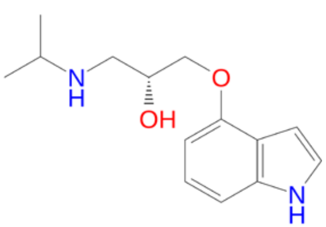

1-Naphthol
NAPHOL01

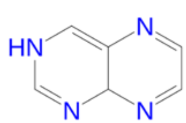

Clozapine
NDNHCL01

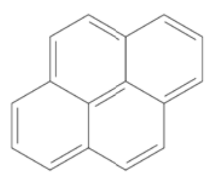

Nicotinic acid
NICOAC02

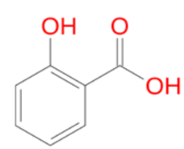

Mefenamic acid
XYANAC

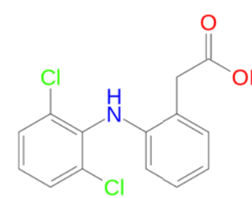

Niflumic acid
NIFLUM10


Pindolol
PINDOL

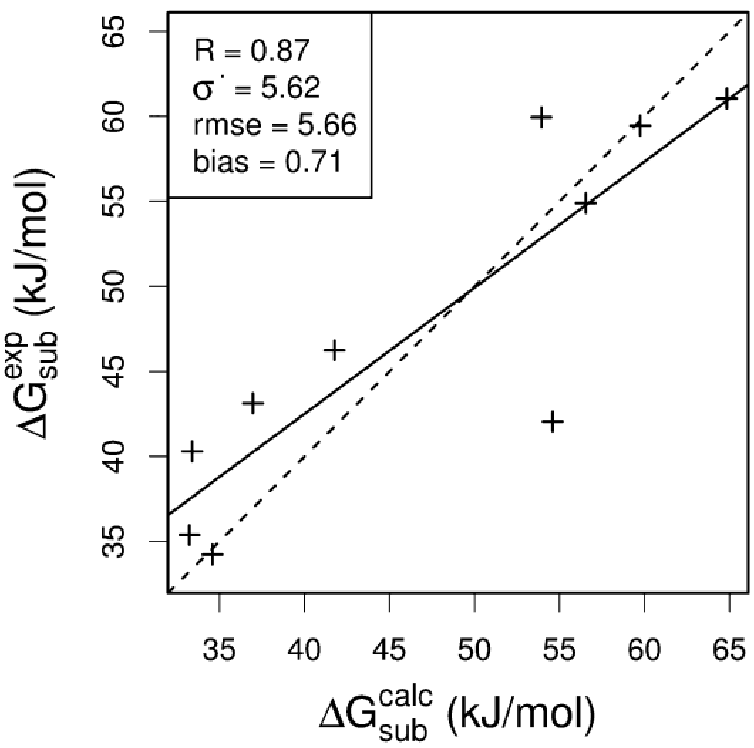

Pteridine
PTERID11


Pyrene
PYRENE07


Salicylic acid
SALIAC

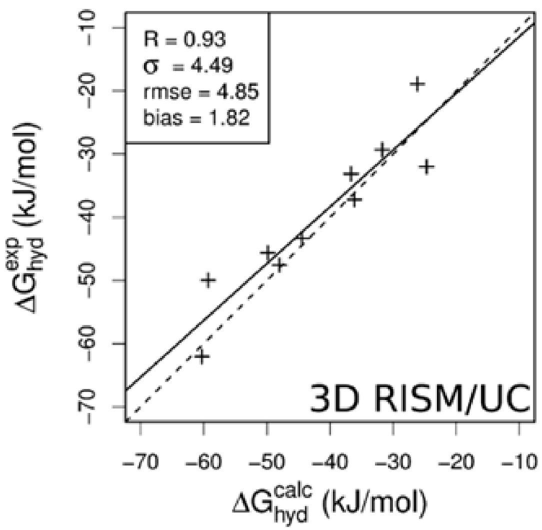

Diclofenac
SIKLIH01

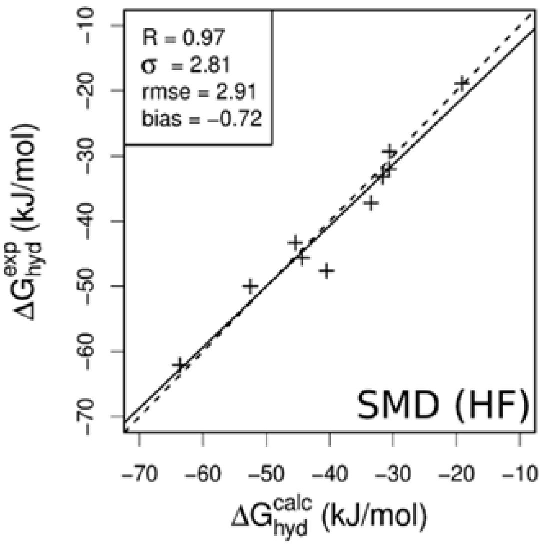
Sublimation free energy predictions



- Validation of the sublimation free energy prediction.
- B3LYP/6-31G(d,p) multipole.
- FIT repulsion dispersion potential.
- Correlation coefficient (R) 0.87.
- RMSE 5.66kJ/mol.

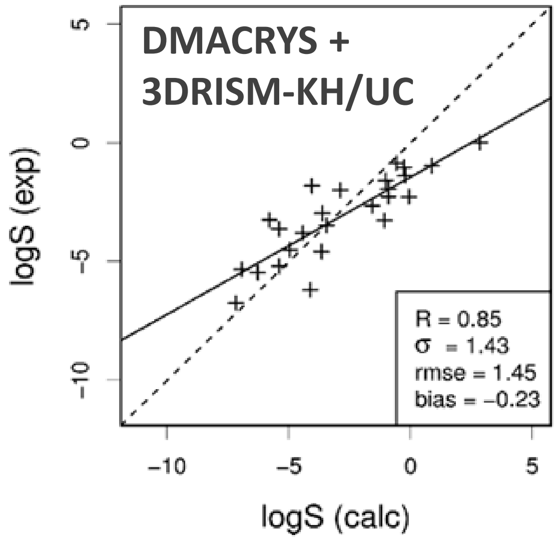
Hydration Free Energy Predictions

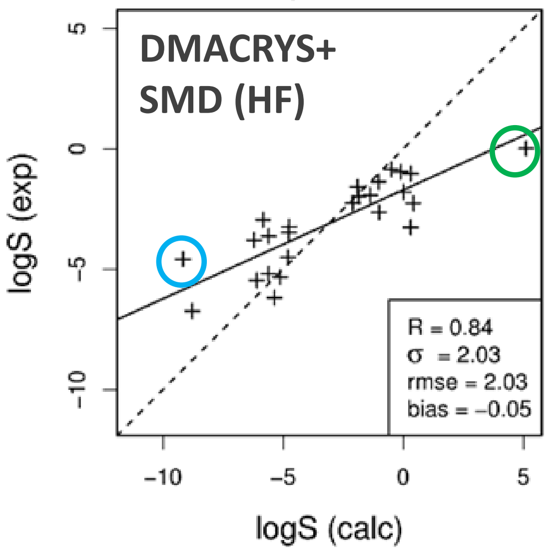




- Validation of the hydration free energy predictions.
- SMD HF/6-31G(d,p).
- Both have strong R values 0.93 RISM, 0.97 SMD.
- RISM has a significantly higher RMSE 4.85kJ/mol RISM, 2.91kJ/mol SMD.

Solution Free Energy Predictions





- The full 25 molecule set is compared to experiment.
- Chemical accuracy ~ 1logS unit. Experimental SD 1.79 LogS.
- Reasonable correlation R 0.85 RISM, R 0.84 SMD.
- RISM method provides best RMSE, RMSE of 1.45LogS RISM, RMSE of 2.03LogS SMD.
- SMD outliers Niflumic Acid and Pteridine.

Palmer, D. S.; McDonagh, J. L.; Mitchell, J. B. O.; van Mourik, T.; Fedorov, M. V., *Journal of Chemical Theory and Computation* **2012**.

To sum up

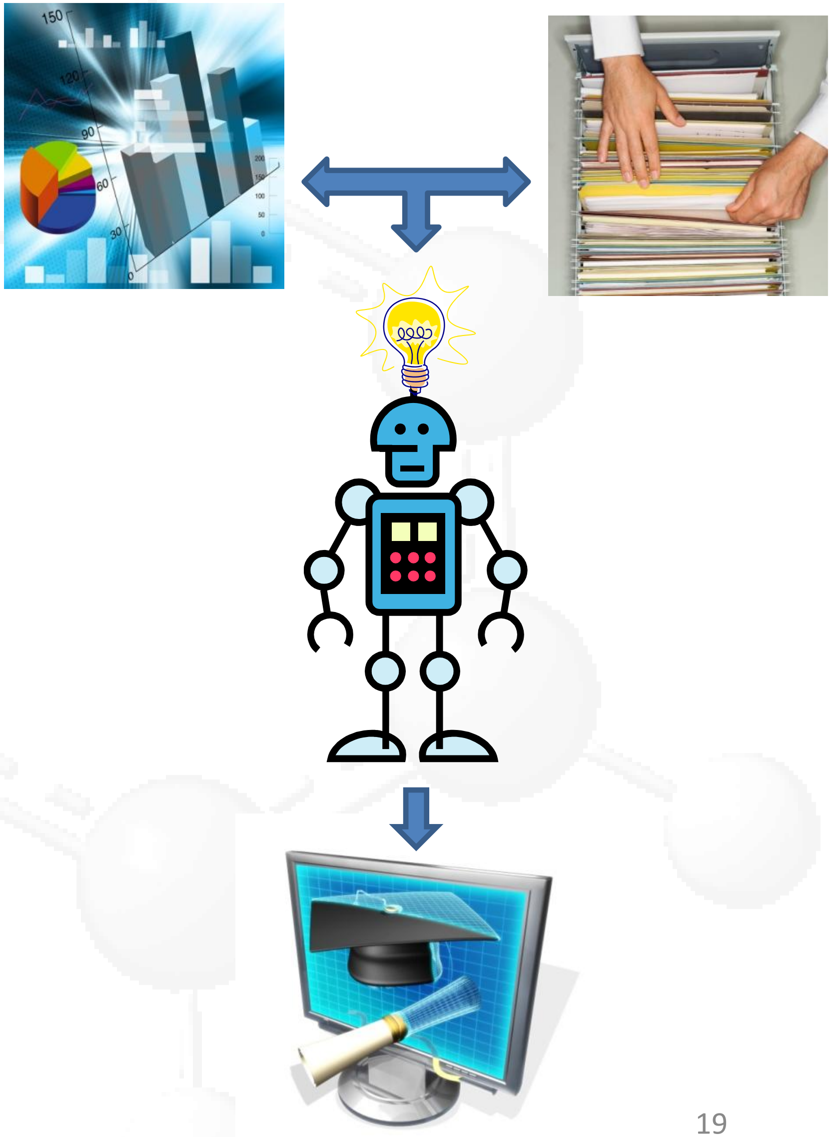
- From these results we concluded it was possible to make predictions of a reasonable accuracy.
- In our methodology a larger portion of error could be attributed to the sublimation free energy prediction.
- Larger datasets were required to fully validate the methodology.

Further models

- We took two approaches to follow up this work:
  - Parameterisation and machine learning approaches to predict ΔG solution.
  - Systematic theoretical improvements in Sublimation free energy predictions. (work currently ongoing).

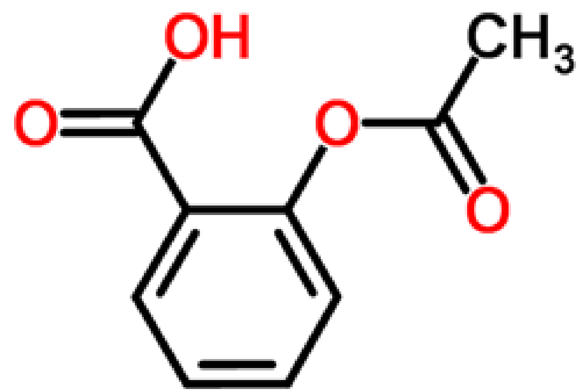
Informatics and machine learning

- We selected a dataset of 100 molecules.
- Calculated descriptors using the chemistry development kit (CDK).
- We followed our previously laid out theoretical methodology for the 100 molecules.
- We combined descriptors and theoretically calculated energies.



Descriptors

- SMILES are input into CDK.
- Structural and some predicted properties are output for use as descriptors.
- These cheminformatics descriptors were used as part of the input for the machine learning methods.

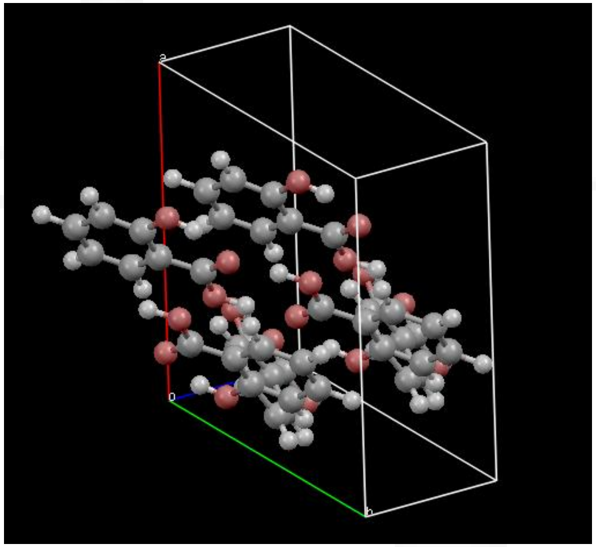


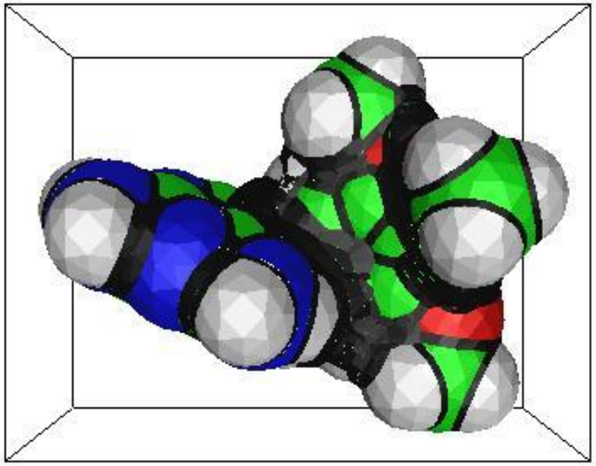
CC(=O)Oc1ccccc1C(=O)O

Descriptor	Value
Molecular Weight	280
Molecular Formula	C9H8O4
XLogP	1.24
Freely rotatable bonds	3
H bond acceptor	4
…..	…..
……	……

Computational Chemistry Calculations

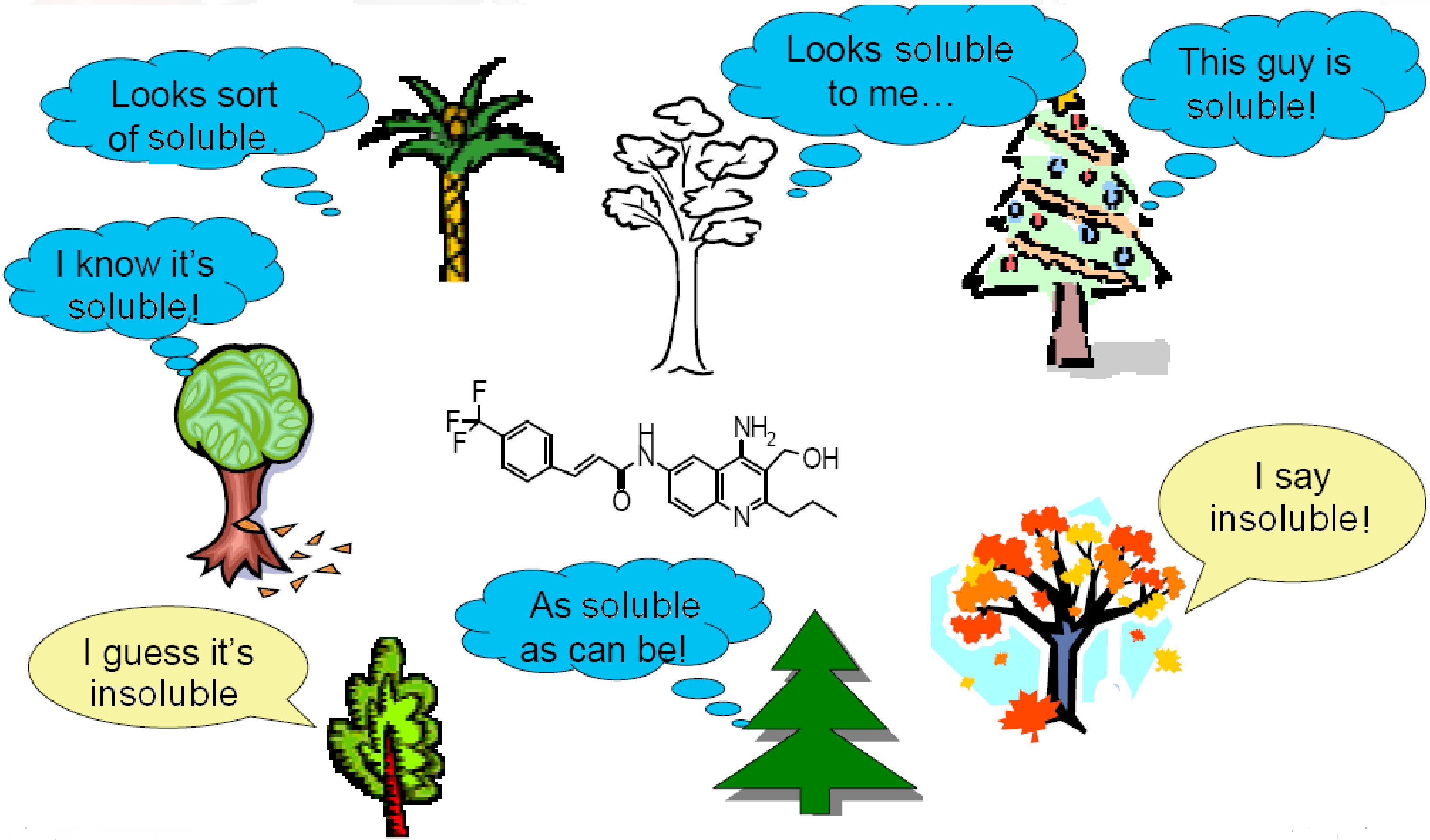
- DMACRYS –B3LYP/ 6-31G(d,p), FIT potential.
- SMD with HF/6-31G(d,p)
- The same level of theory was used in the gas phase as the solution phase.
- SMD selected over RISM as it provided a better correlation in the previous work.



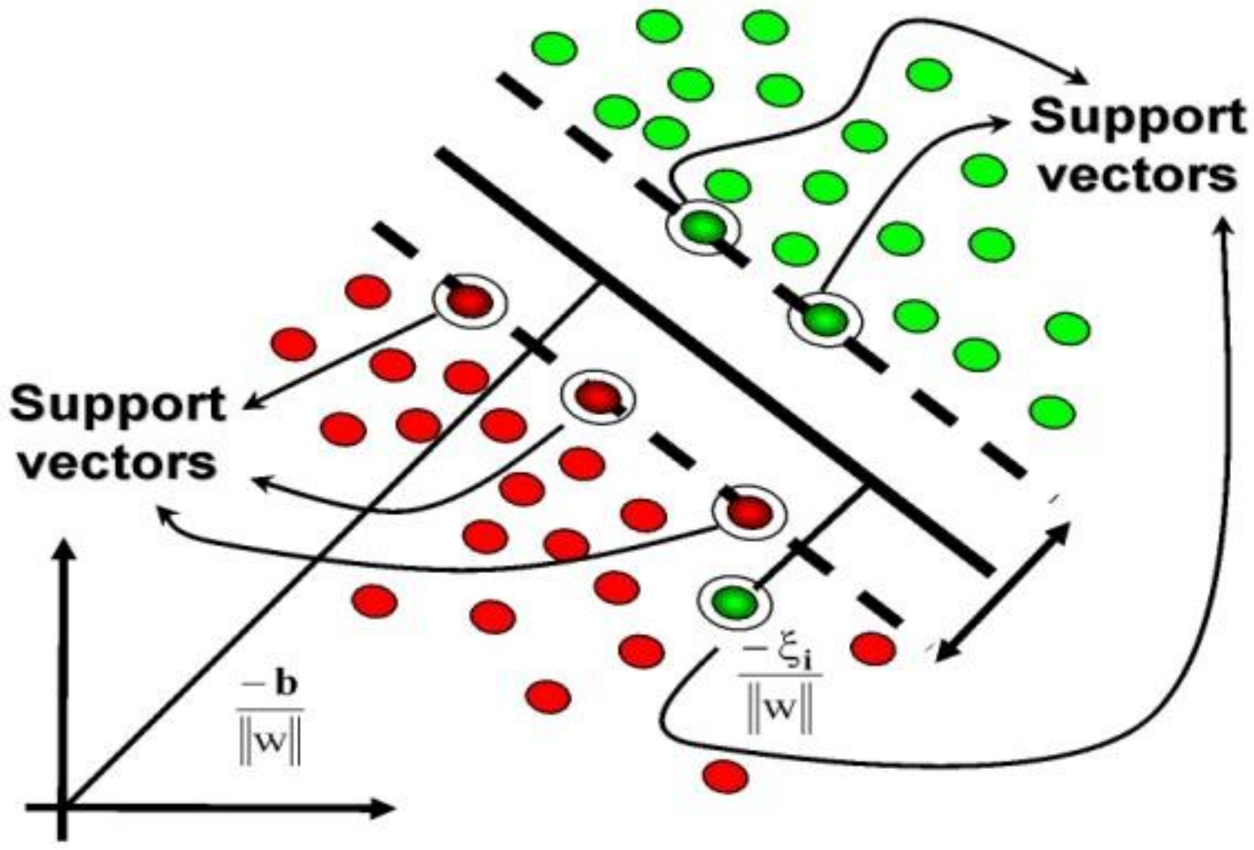


Machine Learning Models

- Random Forest (RF) – A forest of decision trees.



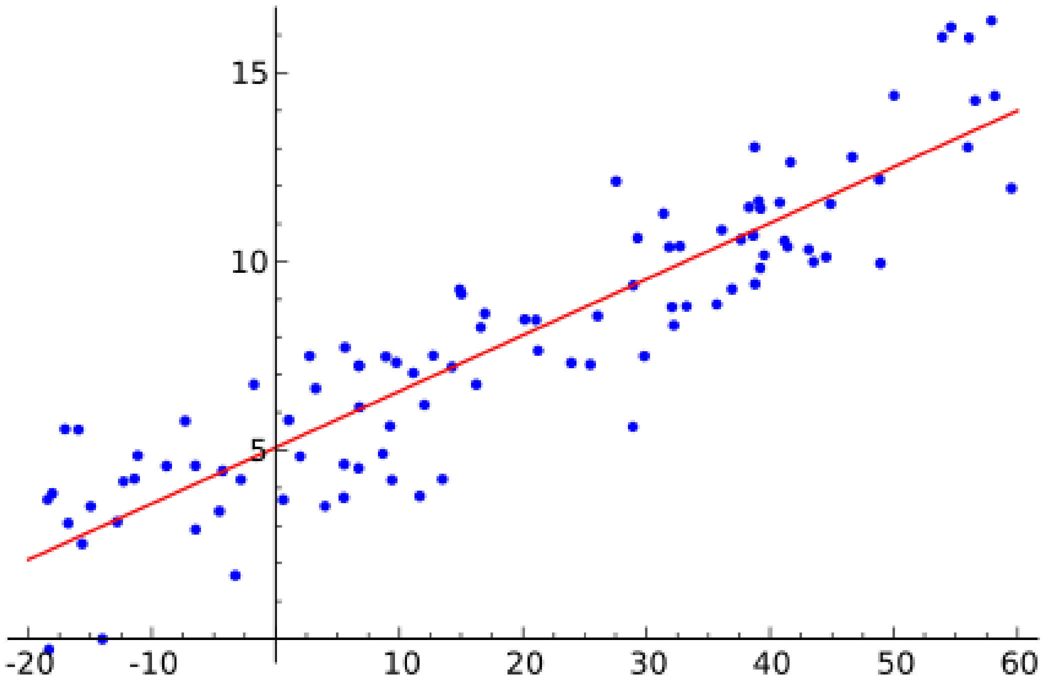
- Support Vector Machines (SVM) – Classification by projection into a higher space and separation by a hyperplane.



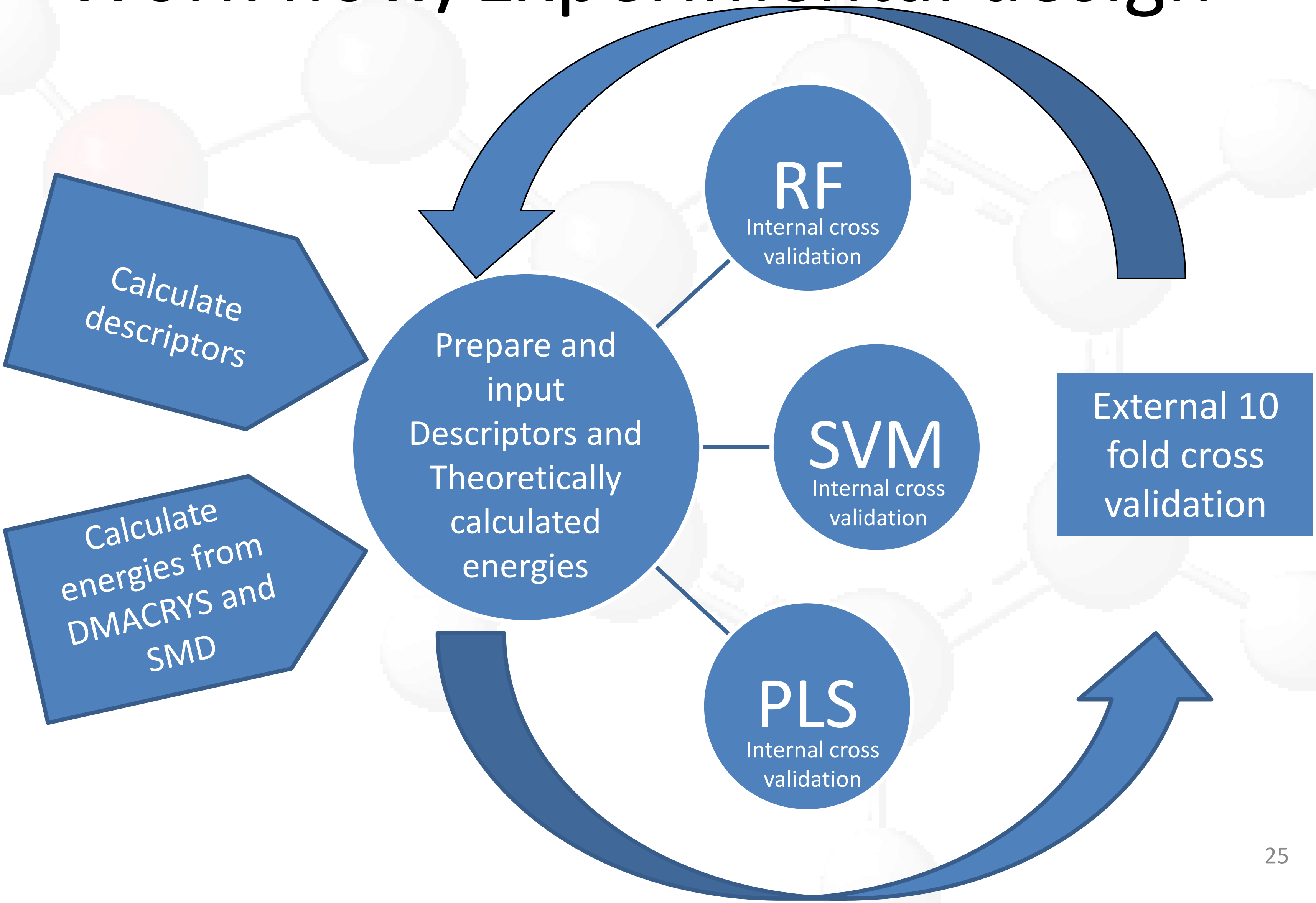
- Partial least squares Regression (PLS) – can be considered as classification by deflation.

$$y = X\hat{b} + \epsilon_t$$

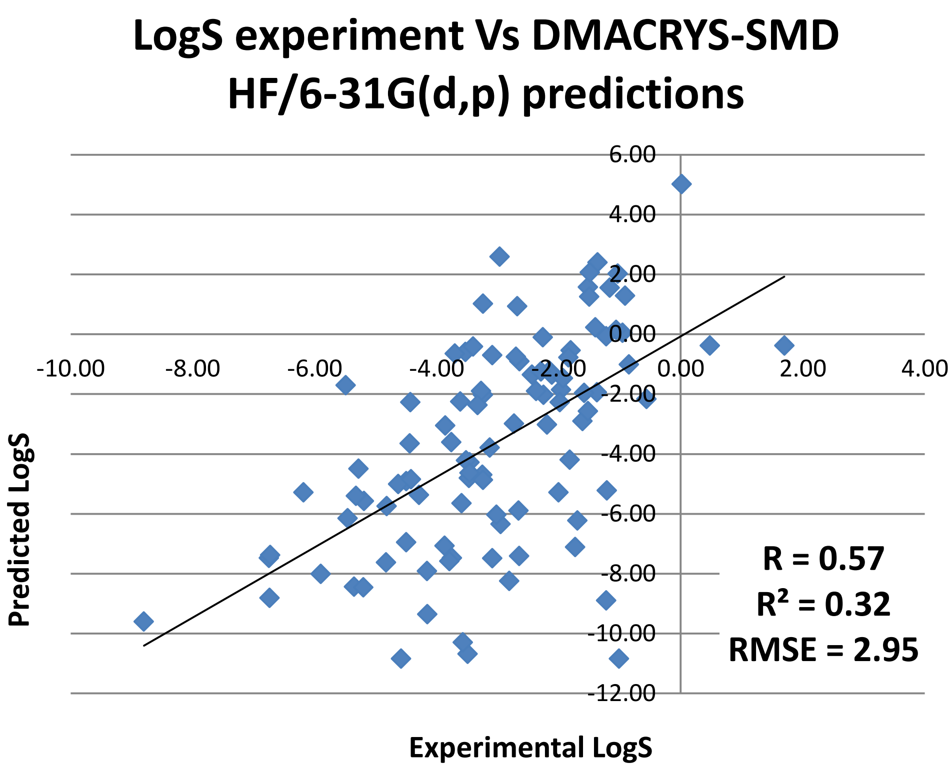
$$\begin{pmatrix} 1 & 0.5 & \color{red}{5} \\ 1 & 0.7 & \color{red}{7} \\ 1 & 0.9 & \color{red}{9} \end{pmatrix} \begin{pmatrix} 50 \\ 70 \\ \color{red}{2} \end{pmatrix}$$



Work flow/Experimental design

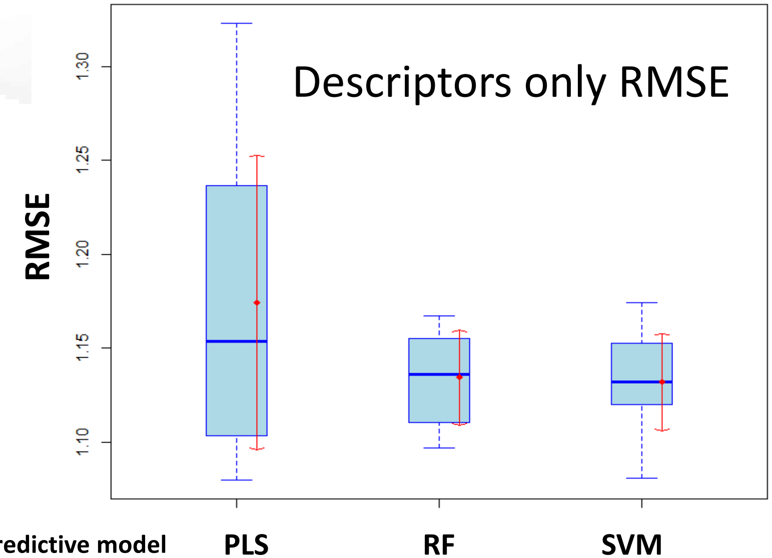


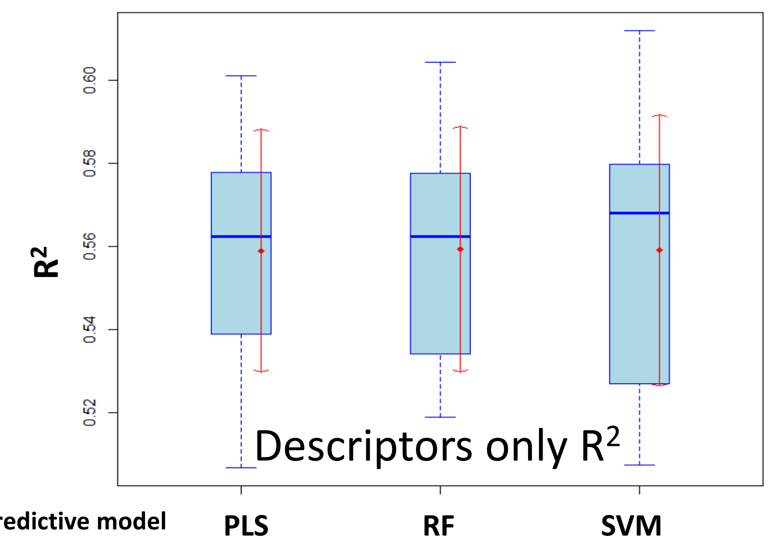
Results



- <u>Results of the purely theoretical prediction</u>.
- Our results are correlative.
- Standard linear regression is a poor fitting model.
- Chemical accuracy ~1logS unit.
- Experimental SD 1.71 LogS units.

Descriptors only

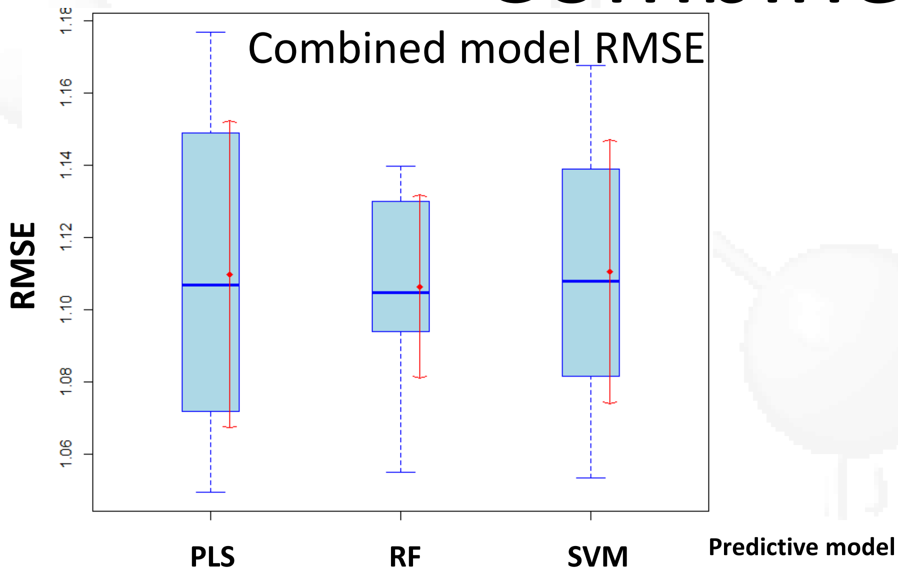


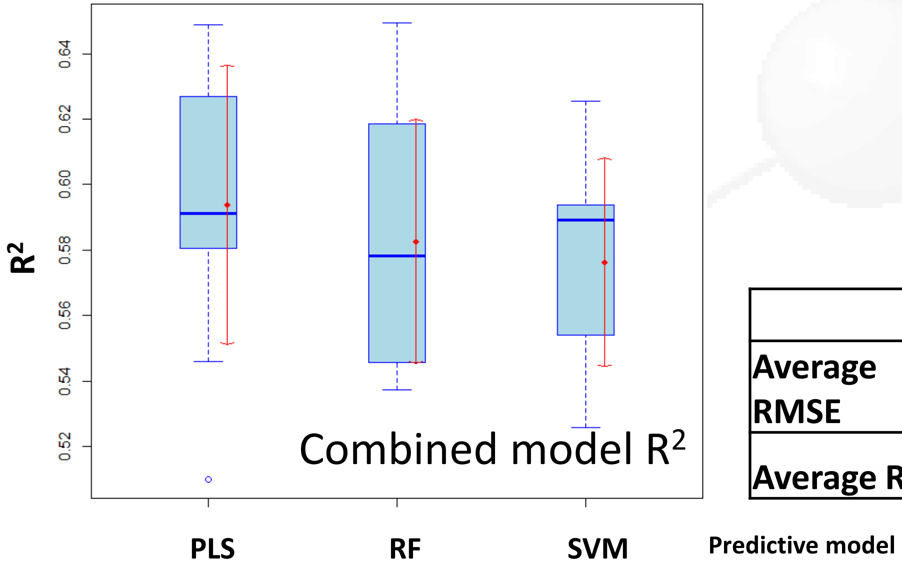


- Results of prediction exclusively using the CDK descriptors.
- All machine learning methods perform better than theory alone.
- Red bars show the SD and mean result.
- Boxes represent 75% of the predictions. Dark blue line shows the median.

	PLS	RF	SVM	Theory
Mean RMSE	1.174(±0.08)	1.134(±0.03)	1.132(±0.03)	2.95
Mean R^2	0.56(±0.03)	0.56(±0.03)	0.56(±0.03)	0.32

Combined model





- The model contains HF/6-31G(d,p) energies and descriptors.
- All show improvement over pure theory.
- Result are similar to those of the descriptors alone.
- Experimental SD 1.71 LogS units.

	PLS	RF	SVM	Theory
Average RMSE	1.110(± 0.04)	1.107(±0.03)	1.111(±0.04)	2.95
Average R^2	0.594(±0.04)	0.583(±0.04)	0.576(±0.04)	0.32

Summary

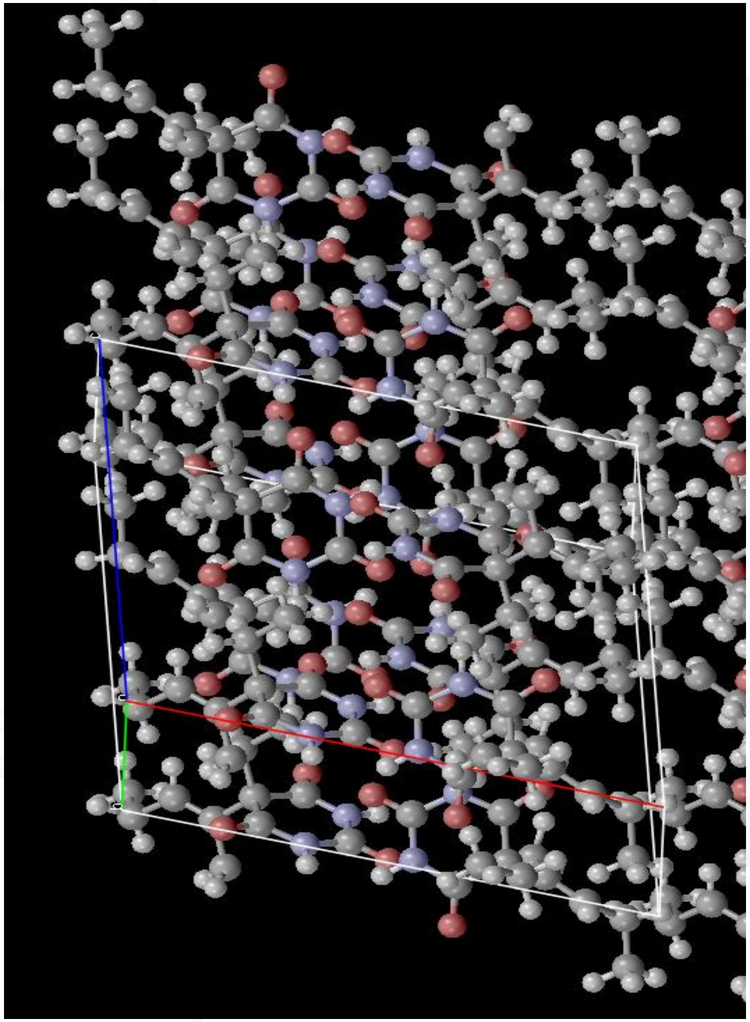
- The information from theoretical calculations at this level has a minor impact but does improve accuracy and correlation of the results.
- The descriptors already hold much of the information.
- Further exploration of models of this type could allow us to find information not held in the descriptors that is accessible by chemical calculation.

Exploration of sublimation free energy prediction

- The largest source of error in the initial method was the sublimation free energy prediction.
- We have a dataset of 60 molecules.
- We made sublimation free energy predictions using this dataset with our previously outlined method.
- We look to DFT methods to provide improved predictions.

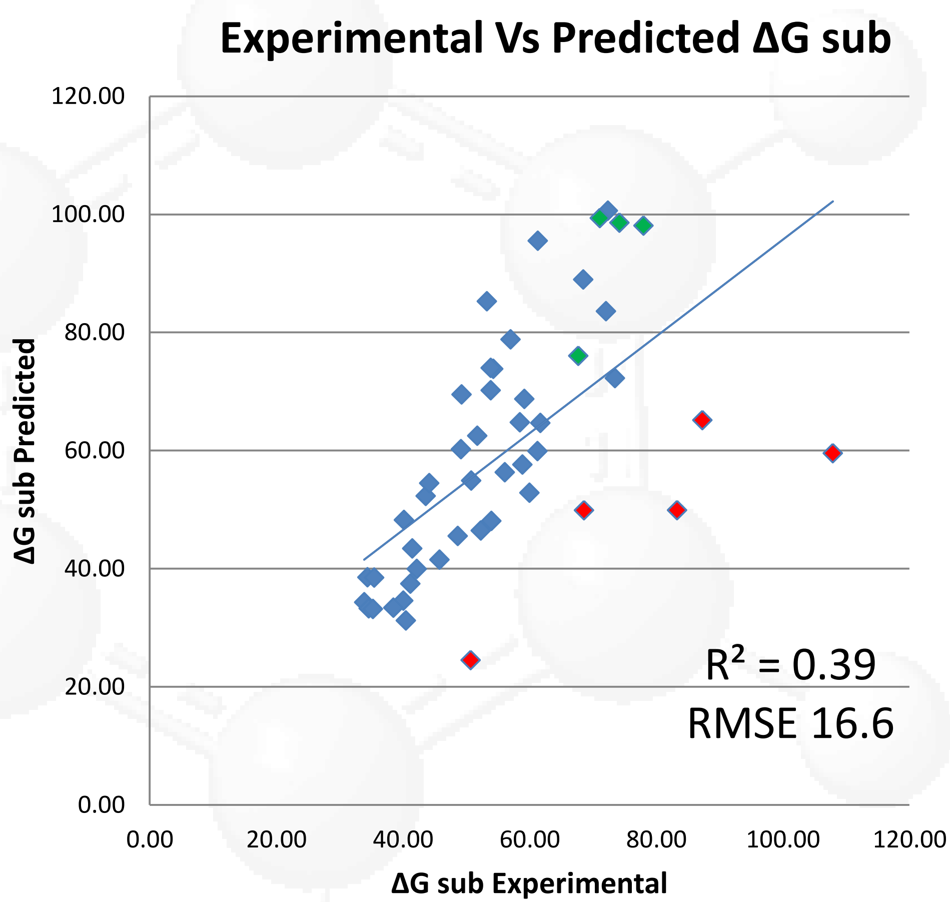
Periodic DFT

- We are using Periodic DFT to make sublimation free energy predictions.
- We are exploring dispersion corrections.
- We will look at the accuracy of prediction of the components of the free energy.



Free Energy of Sublimation

- From our initial methodology.
- A poor correlation.
- Significant RMSE.
- Outliers hold significant leverage.
- All outliers contain NO_2 groups (in red) which are known to be difficult to represent accurately in force fields.



Summary

- We have explored a purely theoretical methodology for predictions of solvation free energy.
- We have expanded from this to produce a combined computational chemistry - cheminformatics methodology.
- We have begun exploration of sublimation free energy, due to the large error it contributed in our original methodology.

Thanks for your attention

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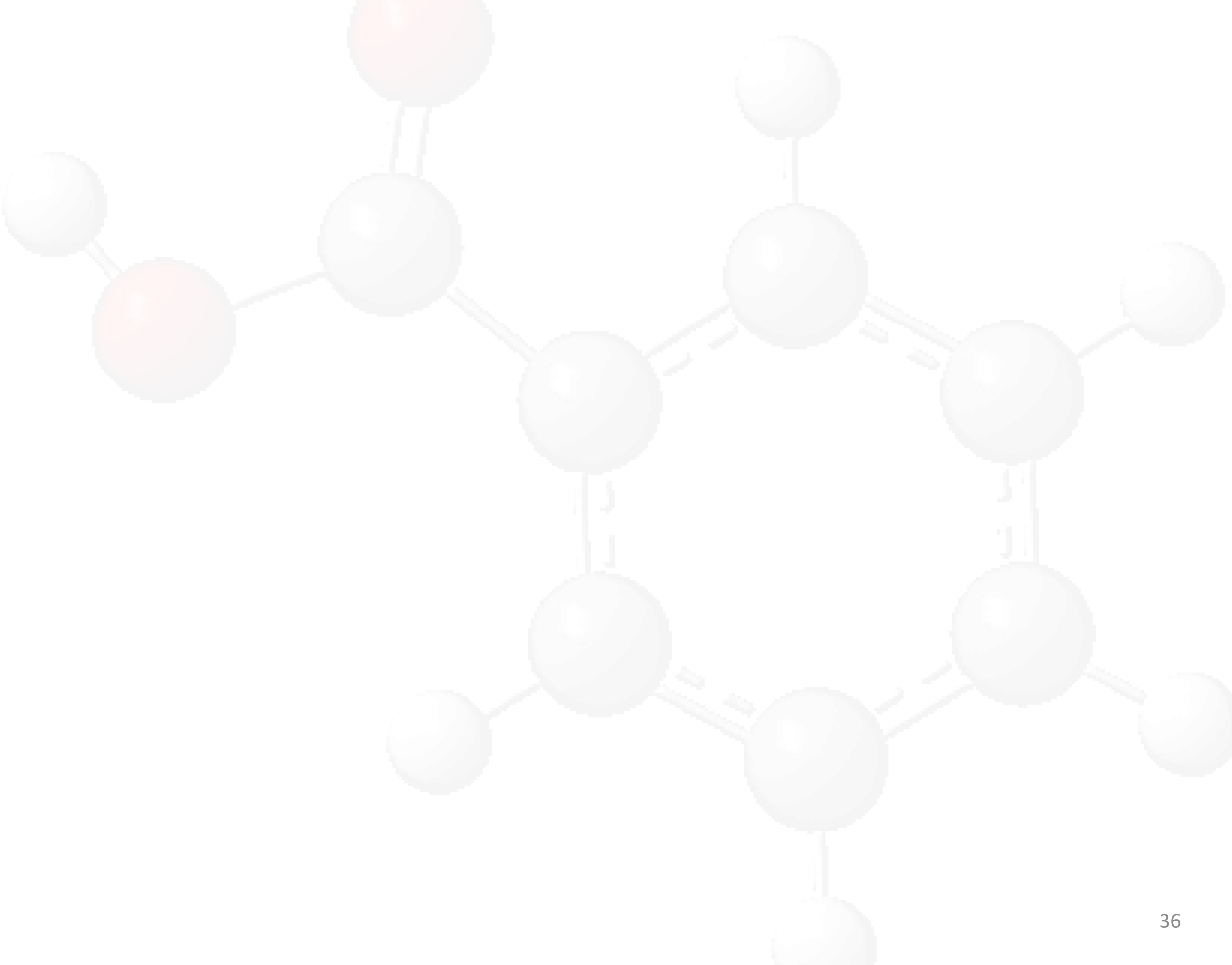
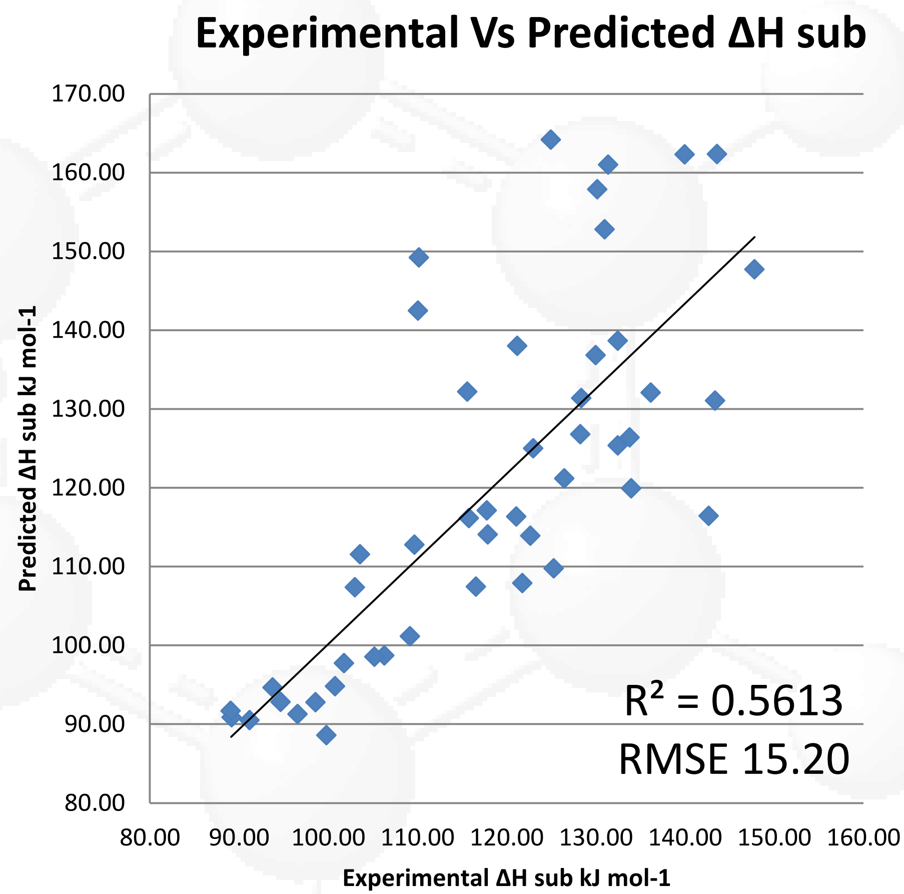


Current Preliminary Results

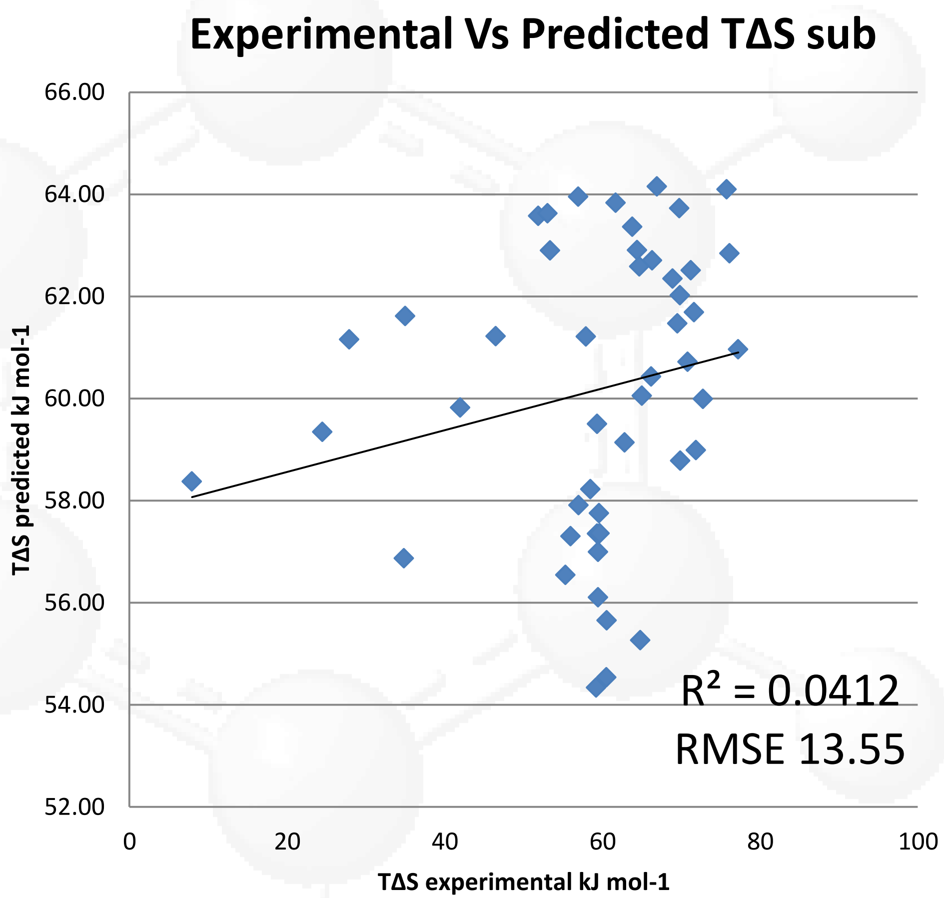
Enthalpy of Sublimation

- Using DMACRYS – B3LYP multipoles FIT potential and Gaussian 09.
- 48 molecules.
- A fair correlation but significant RMSE.



Entropy of Sublimation

- Crystal entropy calculated in DMACRYS, gas phase in Gaussian 09.
- No meaningful correlation.
- Significant RMSE.
- 48 molecules



Additional notes

- Buckingham potential
  $E_{lk} = Bexp(-Cr_{lk}) - Ar_{lk}^{-6}$
- Universal correction
  $\Delta G_{hyd}^{3DRISM-UC} =$
  $\Delta G_{hyd}^{3DRISM} + a(\rho V) + b$
- LogS
  $\frac{\left(\frac{\Delta G_{sol}}{-RT}\right)}{\ln(10)}=\log(S)$
  $\Delta G_{solu} = -RTlnS$
- 1logS unit = 5.71 in terms of ΔG

- Thermodynamics
- ΔH_{sub} = $-U_{latt}$ +2RT
- ΔS_{sub} = $(S_r+S_t) - S_{crys}$
- ΔG_{sub} = ΔH_{sub} - $T\Delta S_{sub}$
- ΔG_{hyd} = $E_{sol} - E_{gas}$
- ΔG_{solu} = $\Delta G_{sub} + \Delta G_{hyd}$
- $\Delta G^{GF} =$
  $K_B T \sum_{\alpha=1}^{Nsolvent} \rho_\alpha \int_{R^3} \left[c_\alpha(r) - \frac{1}{2} c_\alpha(r) h_\alpha(r)\right] dr$

$$\Delta G_{sol}^{o} = \Delta G_{sub}^{o} + \Delta G_{hyd}^{o} = -RTln(S_0 v_m)$$

Molar volume of the crystal Vm

Intrinsic solubility So