



IAF's
**Empirical descriptors for non-covalent
interactions**

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Outline

- ◆ **Why do we need a new descriptor**
- ◆ **Definition of Interactions**
- ◆ **Definition of *IAF's***
- ◆ **Applications for *IAF's***
- ◆ **Summary**



Quantitative Drug Design

A wish list for a new descriptor

- ◆ **Quantitative *cf.* physical property descriptors**
- ◆ **Simple *cf.* topological descriptors**
- ◆ **Robust - not influenced by conformations**
- ◆ **Chemically intuitive *cf.* pharmacophores**

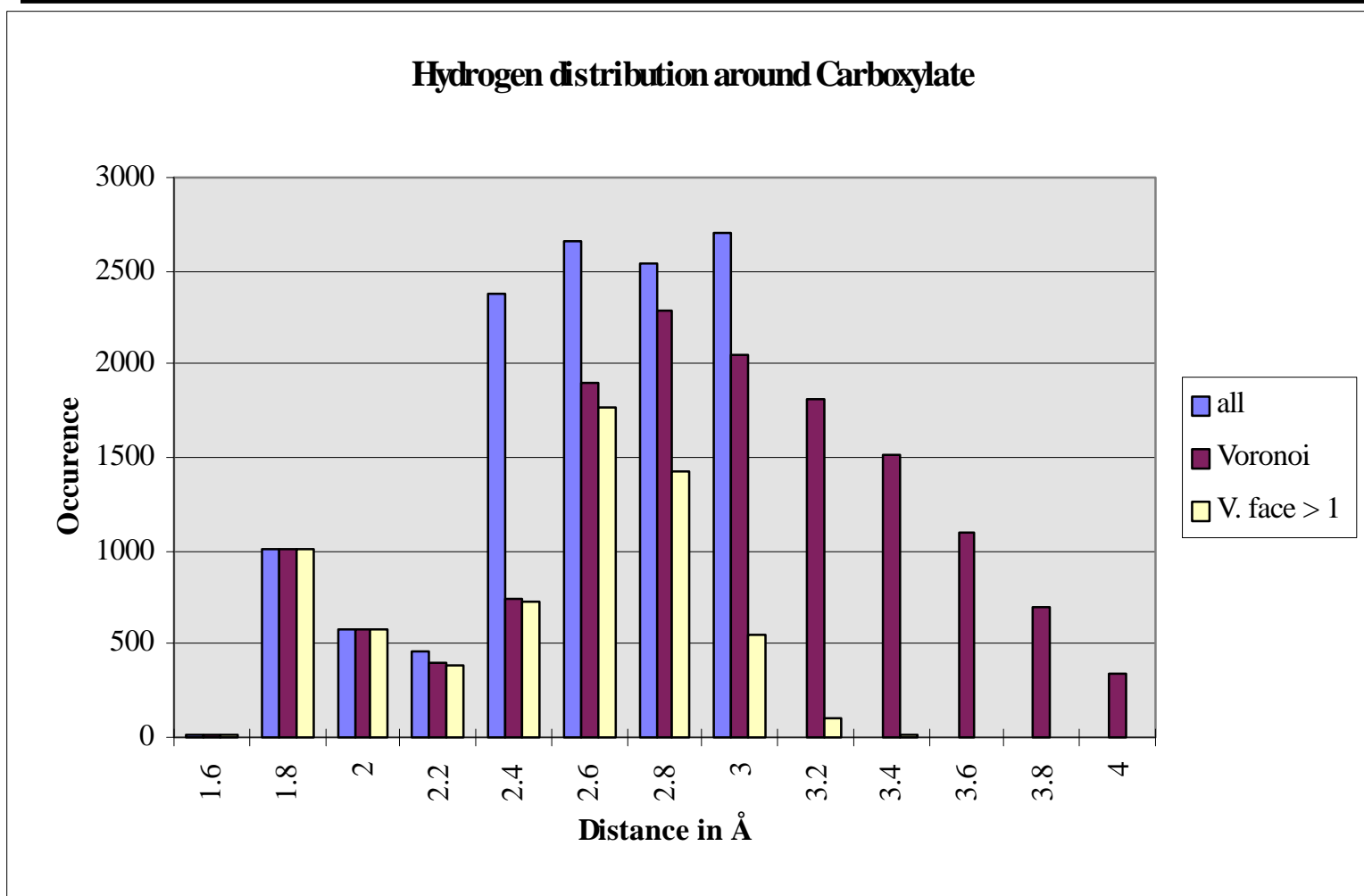


How to fulfil the wish list

- ◆ **An empirical descriptor**
- ◆ **Based on real data**
 - **the Cambridge Structure Database**
 - **crystals - a frozen snapshot of interactions**
 - **180.000+ structures**
- ◆ **Let's do some data mining**

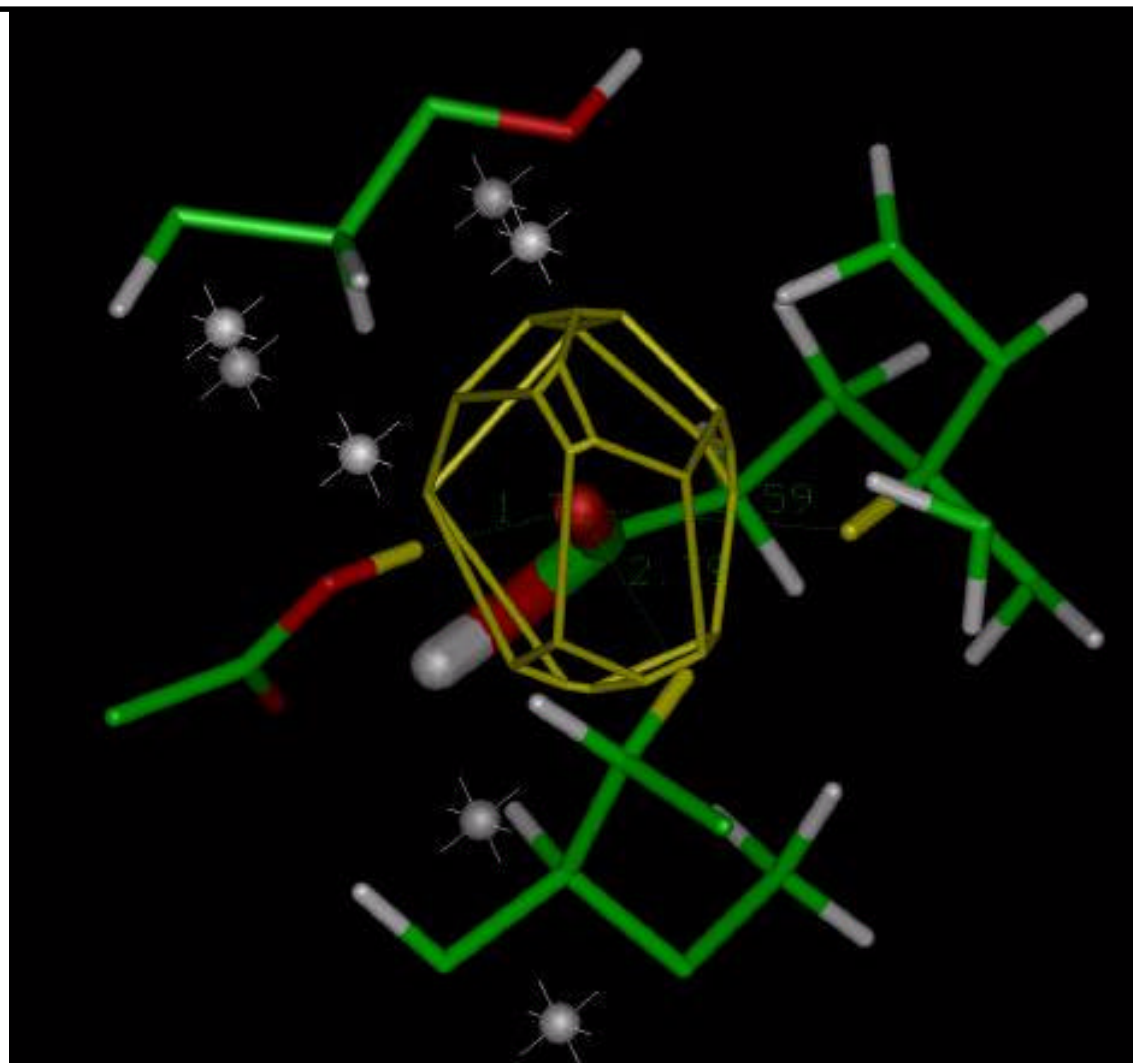


Distribution of distances





The Voronoi Polyhedra



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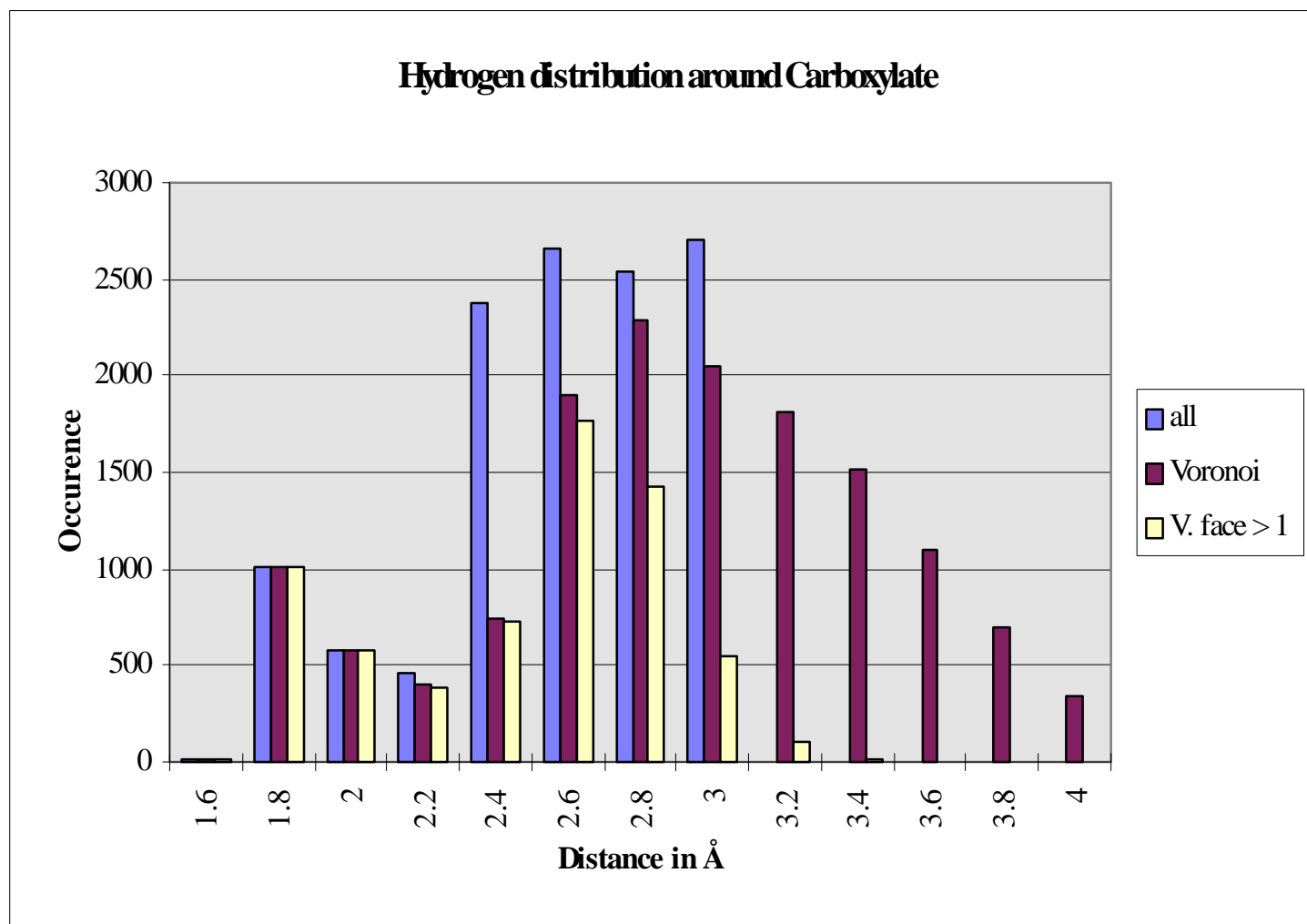


How is an interaction defined

- ◆ **The space in a crystal is divided into atomic areas (concept of Voronoi)**
- ◆ **The ‘shape’ and topology of the atomic areas is used to define interactions**
- ◆ **The mining works robust as a ‘black box’ and isn’t much influenced by minor errors in structural data**



Distribution of distances





What are InterAction Fingerprints

- ◆ **A new empirical descriptor for non-covalent interactions**
- ◆ ***IAF's* are based on the average number of interactions found around atoms in small molecule crystal structures**
- ◆ **They can be determined for any functional groups which is sufficiently represented in the CSD**



Acceptors (fingerprints 1-3)

- ◆ **F1**
 - **O...H-distance below 185 pm or interactions to metals (salt bridges, charged acceptors)**

- ◆ **F2**
 - **O...H-distance between 185 and 220 pm (traditional hydrogen bonds)**

- ◆ **F3**
 - **O...H above 220 pm (mainly C-H...O)**



Neutral interactions (fingerprint 4)

- ◆ **F4**
 - **mainly H...H contacts, but also Hal...Hal interactions fall into this category (pure van-der-Waals interactions, packed atoms)**



Donors (fingerprints 5-7)

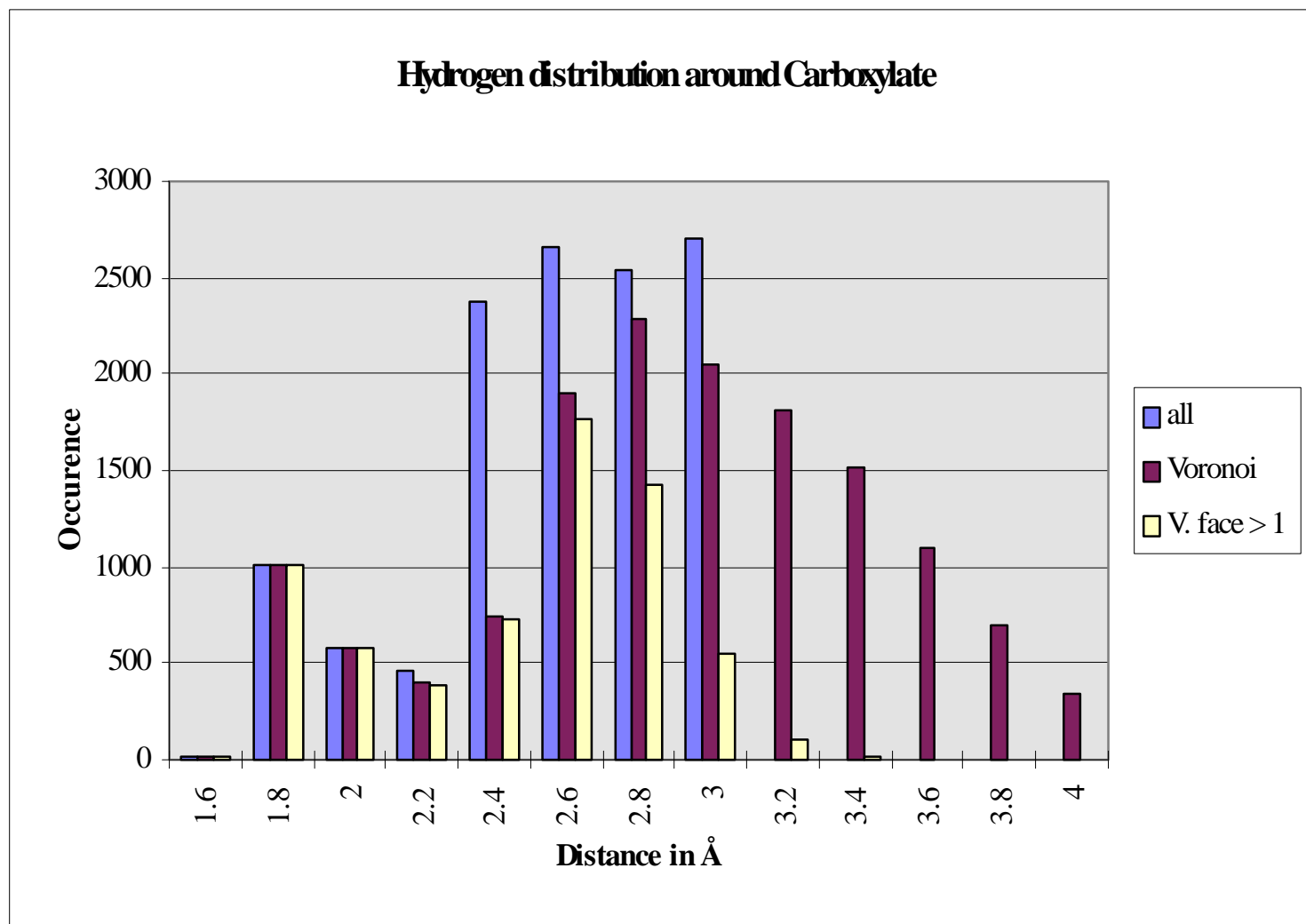
- ◆ **F7**
 - **O...H-distance below 185 pm or interactions to metals (salt bridges, charged donors)**

- ◆ **F6**
 - **O...H-distance between 185 and 220 pm (traditional hydrogen bonds)**

- ◆ **F5**
 - **O...H above 220 pm (mainly C-H...O)**



Distribution of distances





'Fuzzy' interactions

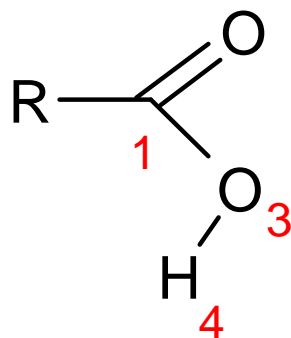
- ◆ **F8**
 - **The sum of small faces of electronegative atoms to hydrogen**

- ◆ **F9**
 - **The sum of small faces of electronegative atoms to other electronegative atoms**

- ◆ **Rationale: Aromatic interactions or groups - atom interactions are otherwise ignored**



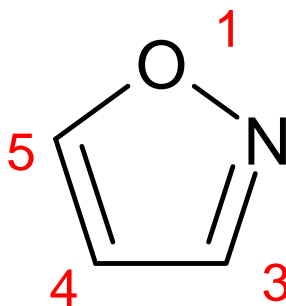
IAF - example I



Atom	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0.00	0.00	0.02	0.00	0.00	0.00	0.00	0.54	0.46
2	0.54	0.32	1.83	0.00	0.00	0.00	0.00	1.65	0.76
3	0.02	0.03	1.29	0.00	0.00	0.00	0.00	1.38	0.59
4	0.00	0.00	0.00	0.90	0.10	0.04	0.94	0.00	0.00



IAF - example II



Atom	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0.00	0.01	1.37	0.00	0.00	0.00	0.00	1.30	1.05
2	0.13	0.20	1.17	0.00	0.00	0.00	0.00	1.20	0.79
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.53	0.56
4	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.57	0.40
5	0.00	0.00	0.05	0.00	0.00	0.00	0.00	0.49	0.51



Usage of IAF's

- ◆ **Simple to implement in computational programs as atomic fingerprints add up to groups or molecules**
- ◆ **Measure of bioisostereoisom and similarity (same fingerprint should produce same interactions)**
- ◆ **Correlation with physical properties seems to work**



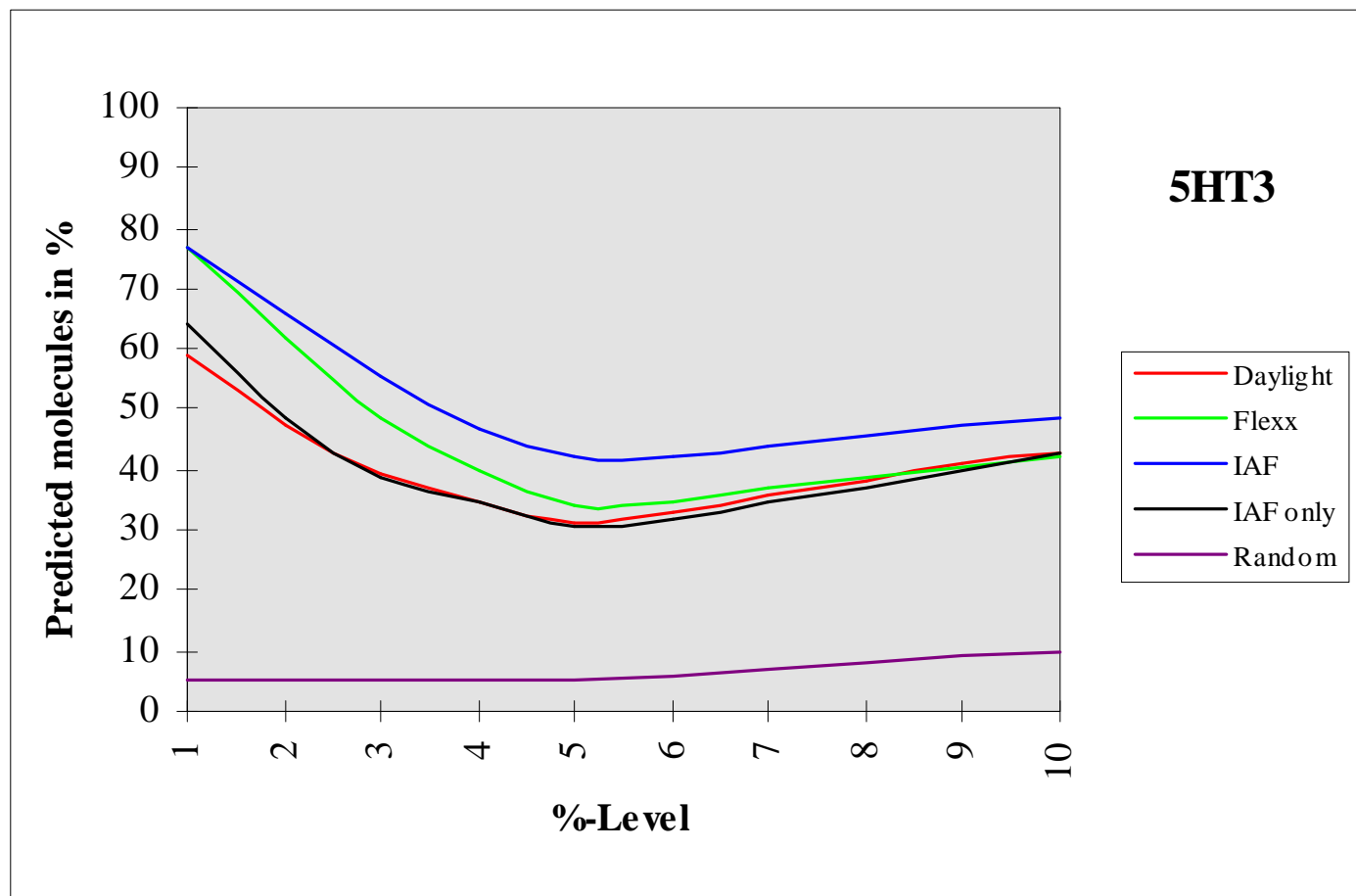
Application I Similarity calculations using FTree

- ◆ **Similarity calculation on an molecule by molecule basis**
- ◆ ***IAF's* as numerical data - FTree to calculate the similarity**
- ◆ **Tested for 5 sets of active inhibitors and a random dataset**
- ◆ **On average 20% gain to Daylight 2D fingerprints**



Application I

Similarity calculations using FTree





Application II logP calculations

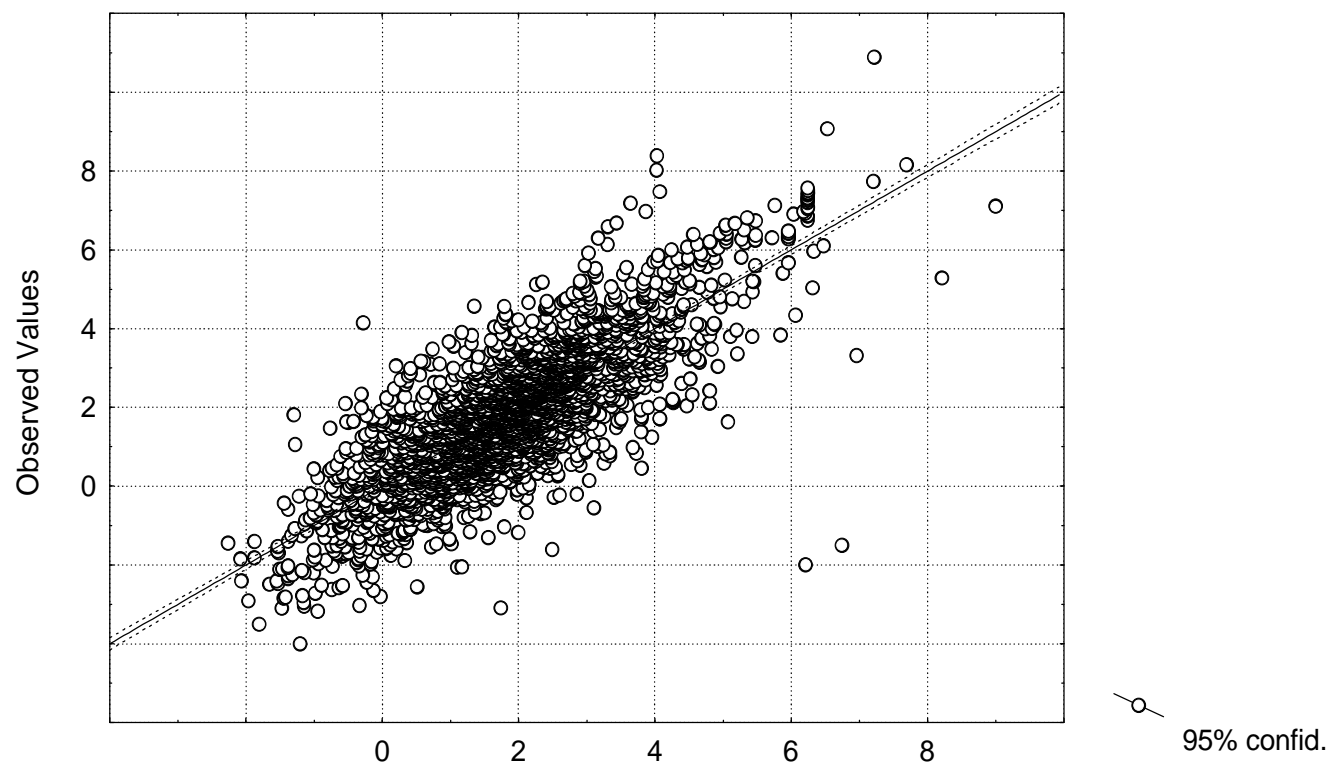
- ◆ **A correlation with physical data**
- ◆ **1/3 of logP Star dataset**
- ◆ **simple linear regression (EXCEL)**
- ◆ **no correction factors**



Application II

logP calculations

Predicted vs. Observed Values
Dependent variable: VAR2



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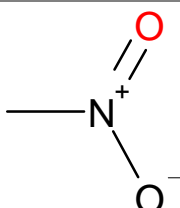
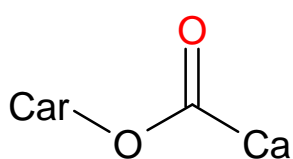
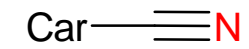
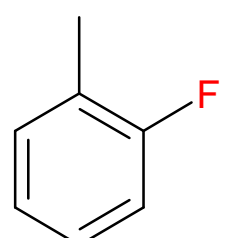
Application III Biostere Prediction

- ◆ **An atom to atom based comparison**
- ◆ **Same *IAF* should produce the same interaction environment**
- ◆ **Same comparison function as in FTree**
- ◆ **Transferable between different atom types**



Application III

Bioisostere Prediction

Atom	Similarity	Strong Acceptor	Acceptor	Weak Acceptor
	1.000	0.03	0.05	2.24
	0.956	0.03	0.03	2.51
	0.938	0.01	0.04	2.09
	0.922	0.00	0.05	3.00



Summary

- ◆ ***IAF's* are quantitative**
- ◆ ***IAF's* are simple**
- ◆ ***IAF's* are robust**
- ◆ ***IAF's* are chemical intuitive**
- ◆ ***IAF's* are interpretable**



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