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Choosing the Right Similarity Measure

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Overview

- Bias fusion of similarity coefficients
- Machine learning approach
- Design your own coefficient
- Fusion of fingerprint pathlengths
- Non-hierarchical k-modes algorithm

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Similarity Coefficients

- Originally used 22 coefficients
- Results of searches clustered to identify similar coefficients
- 13 identified as unique
- Relative performance of each appears to be size dependent

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Size Dependency

- MDDR sorted by bit density
- Divided into 20 equal partitions
- One compound from middle of each partition used as query
- All 13 coefficients used
- Best performing coefficient deduced for each partition

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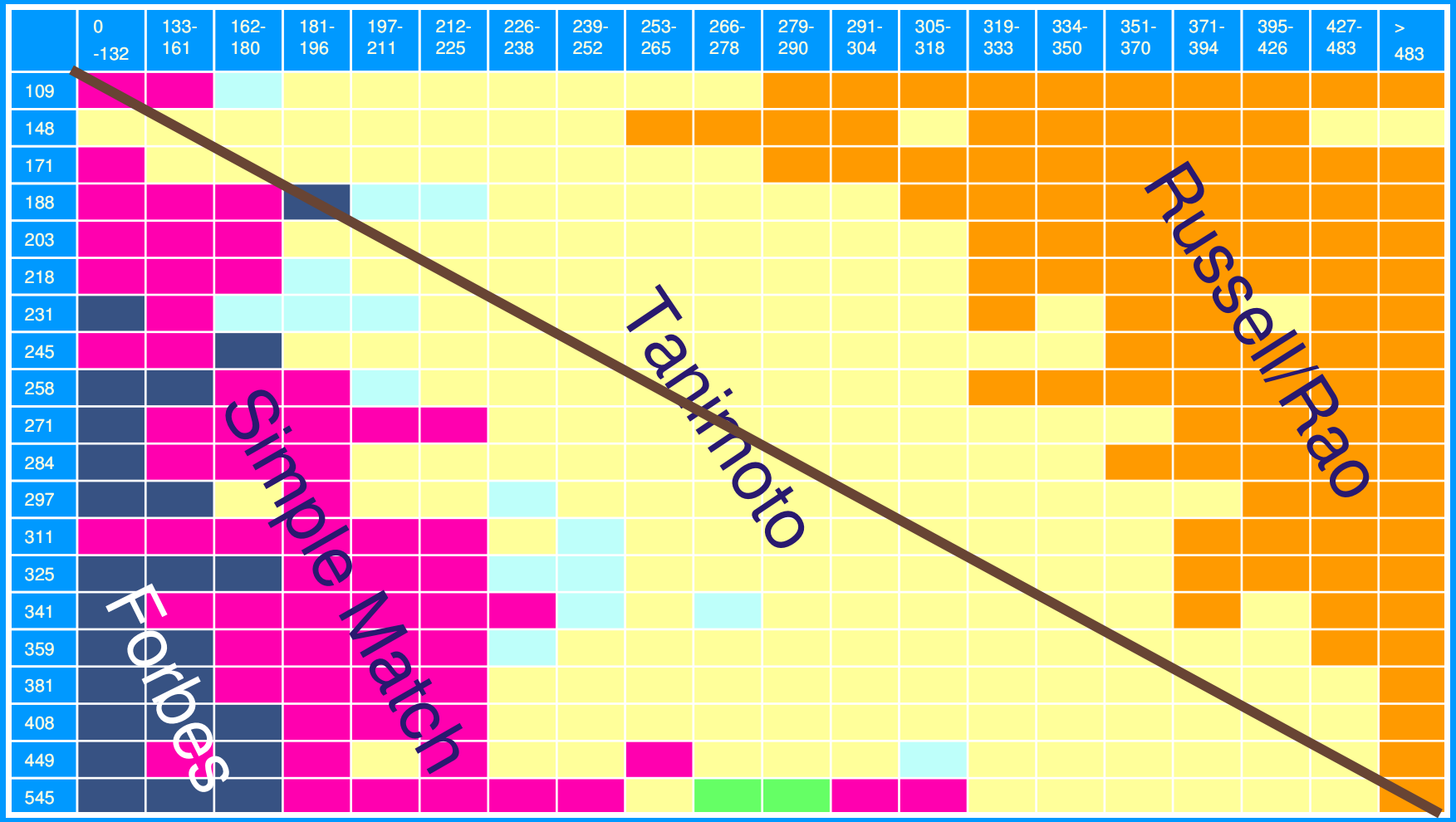
Size dependency



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Size dependency

Size Range	Tan	Rus	SM	Bar	Cos	Ku2	For	Fos	Sim	Pea	Yul	Sti	Den
0-100	1	0	31	1	1	1	21	1	5	1	8	1	1
101-150	15	0	93	28	13	14	72	13	8	18	33	18	25
151-200	91	6	157	135	83	68	155	79	16	97	114	95	113
201-250	158	22	83	175	123	90	117	123	19	137	113	136	150
251-300	162	89	49	139	155	142	66	155	83	148	125	151	141
301-350	211	214	9	130	224	224	21	225	206	207	175	207	188
351-400	107	189	0	41	130	152	2	131	181	111	83	111	88
401-450	18	124	0	5	35	59	0	35	113	23	18	24	12
451-500	1	78	0	0	12	20	0	12	72	3	4	4	0
>500	0	47	0	0	0	6	0	0	44	0	0	0	0

Retrieval (top 5%) of Antihypertensives - 200 bits

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Data Fusion

- Combine rankings from two or more coefficients
- Rankings combined by MAX or SUM
- Has shown to improve performance
- Choice of coefficients not obvious
- Size dependent & Class dependent

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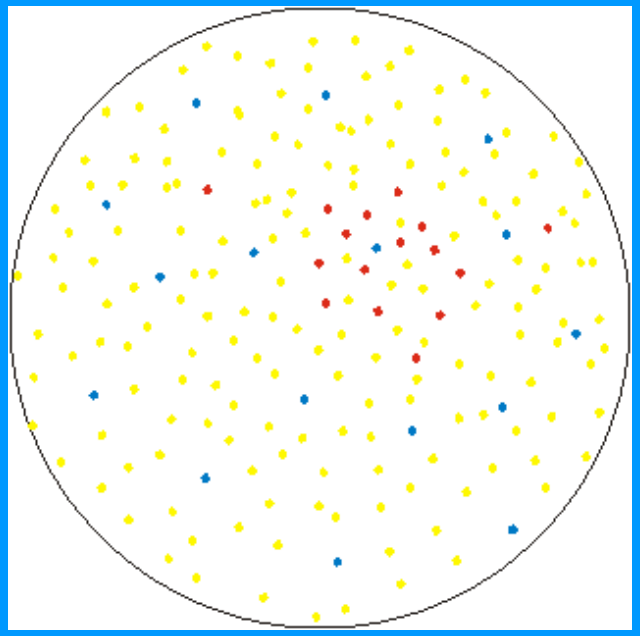
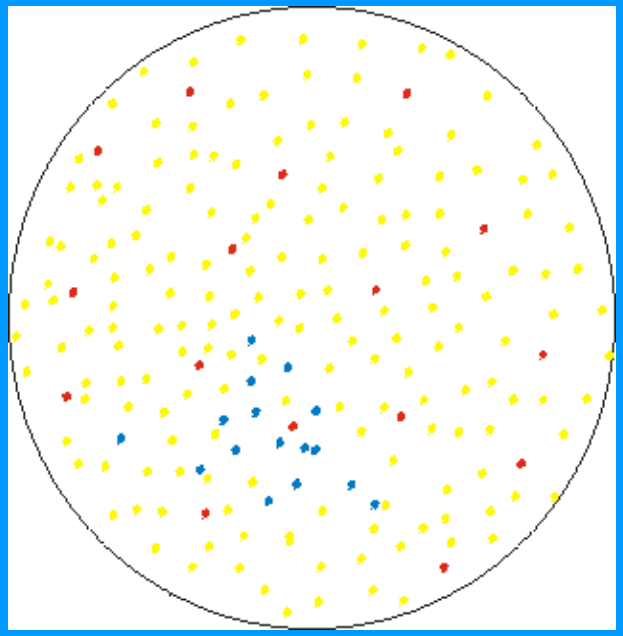
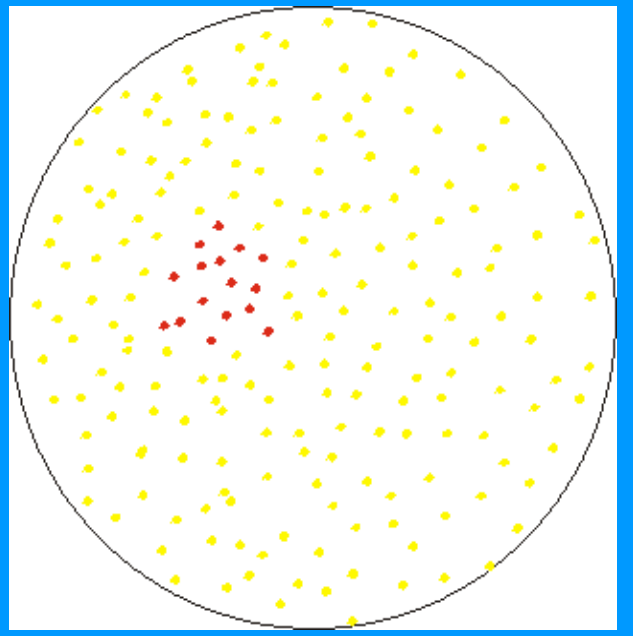
Aims



Russell Space



Forbes Space



Combined Space

Red = Class A, Blue = Class B, Yellow = bulk of DB

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Biasing coefficient selection

- Using four complementary coefficients:

Forbes	Simple Match	Tanimoto	Russell/Rao
$\frac{na}{(a+b)(a+c)}$	$\frac{a+d}{n}$	$\frac{a}{a+b+c}$	$\frac{a}{n}$

- Various weighting schemes used to combine these
  - based on previous search results

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Size dependency

Size Range	Tan	Rus	SM	For
0-100	1	0	31	21
101-150	15	0	93	72
151-200	91	6	157	155
201-250	158	22	83	117
251-300	162	89	49	66
301-350	211	214	9	21
351-400	107	189	0	2
401-450	18	124	0	0
451-500	1	78	0	0
>500	0	47	0	0

Retrieval (top 5%) of Antihypertensives - 200 bits

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Weighted Fusion

- F1 Equal weights - SUM
- F2 Equal weights - MAX
- F3 Number of dominant size ranges - SUM
- F4 Number of dominant size ranges - MAX
- F5 Manually-selected weights
- F6 1.0 for target weight, decreasing by 10% away from this

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Weighted Fusion

Class	Tan	F1	F2	F3	F4	F5	F6
43200	**13**	1.08	1.0	1.0	1.0	1.0	1.0
1200	**7**	1.0	1.0	1.0	1.0	2.0	1.0
75000	**68**	1.0	1.0	1.03	1.0	1.1	1.01
27200	**79**	0.92	0.97	1.0	1.0	0.94	0.97
6200	**109**	0.99	1.0	1.02	1.0	0.83	1.0
72	**73**	1.01	1.01	1.0	0.99	1.01	1.01
7000	**41**	1.56	1.8	1.22	1.0	1.2	1.2
9200	**68**	0.94	0.87	1.0	1.0	1.0	1.0
75000	**39**	1.15	1.13	1.15	1.15	1.03	1.1
2000	**34**	1.03	0.94	1.0	1.0	1.03	1.03
9200	**29**	1.48	1.41	1.07	1.0	1.17	1.03
27200	**216**	1.05	1.04	1.04	0.99	1.01	1.01
75000	**89**	1.0	0.99	0.99	1.0	0.96	0.96
6200	**92**	0.99	0.9	0.97	0.97	1.0	0.97
70000	**234**	0.9	0.83	0.96	1.0	1.0	0.99
31000	**19**	1.11	1.0	1.05	1.21	1.0	1.05
37200	**53**	1.13	1.09	1.23	1.02	1.09	1.15
68000	**245**	0.7	0.62	0.82	0.87	1.0	1.0
2000	**32**	1.38	1.5	1.06	1.0	1.0	1.0

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Machine Learning Approach

- To identify optimum weights for combining coefficients for a given active class
- Training sets of 1000 compounds
  - 70-100 actives
  - Rest made up of random database cmpds

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Machine Learning Approach

- Use actives as queries for each weighted combination
  - Search using every active
  - Search using modal fingerprint
- Weight combination controlled by
  - GA
  - Systematic approach in 4% steps
- Fitness function = Median rank position

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Modal Fingerprint

	1 0 0 1 0 1 1 0 1 0 0 0 1 1 0 1 0 0 1
	1 0 0 0 1 0 1 1 1 1 1 0 1 0 1 1 0 0 1 0
	0 0 1 0 0 1 0 1 1 0 1 0 1 0 0 1 0 1 1 0
	0 1 1 1 0 1 0 0 0 1 0 1 0 0 1 0 1 1 0 1
	1 0 1 1 0 1 0 0 1 0 1 1 0 1 0 0 0 0 0 0
40% threshold	1 0 1 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
60% threshold	1 0 1 1 0 1 0 0 1 0 1 0 0 0 1 0 0 0 0 0
80% threshold	0 0 0 0 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0

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Training set results

Summary of Systematic Results for Fusion (Median)						Median Ranks for Individual Coefs.			
Class	**TanWt**	**RusWt**	**SMWt**	**ForWt**	**Results**	**Tan**	**Rus**	**SM**	**For**
64220	0.20	0.32	0.48	0.00	**38.65**	39.61	41.35	43.58	86.49
78413	0.24	0.20	0.04	0.52	**138.72**	160.65	294.86	151.92	151.50
12200	0.00	0.00	0.20	0.80	**296.87**	349.68	496.74	309.14	297.05
7707	0.00	0.68	0.32	0.00	**47.75**	48.98	49.31	54.67	59.25
44200	0.00	1.00	0.00	0.00	**202.58**	265.12	**202.58**	495.19	472.39
80499	0.00	0.00	0.92	0.08	**193.56**	292.28	566.47	194.12	199.57
59210	0.52	0.00	0.00	0.48	**81.50**	97.51	116.88	100.93	92.80
31281	0.00	0.04	0.96	0.00	**105.65**	188.01	489.38	105.67	134.13
52503	0.00	0.00	1.00	0.00	**215.91**	312.60	514.66	**215.91**	250.12
42710	0.04	0.96	0.00	0.00	**91.49**	95.37	93.44	162.21	168.48

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Test Set Results

Number of Actives on the Top 500					
Class	**Cmpd**	**Tan**	**W1**	**W2**	**W3**
64220	143075	32	31	12	**32**
64220	188743	33	**34**	25	**34**
78413	154230	6	**6**	**6**	4
78413	195947	4	**6**	**6**	**7**
12200	186494	4	**4**	**4**	**4**
12200	174953	4	3	3	1
7707	215004	42	**42**	40	**42**
7707	213232	38	29	**40**	**41**
44200	223448	8	**8**	**8**	7
44200	214248	16	**16**	**16**	**16**
80499	197635	4	**4**	**4**	**4**
80499	257429	5	**5**	**5**	**5**
59210	183938	22	**23**	**22**	**23**
59210	227061	3	**3**	2	**3**
31281	154907	18	**20**	**32**	**31**
31281	143339	24	**30**	**34**	**32**
52503	248597	11	**11**	**11**	**11**
52503	207515	9	**9**	**9**	8
42710	214762	27	**27**	**27**	**27**
42710	200021	7	6	**8**	**8**

W1: Fusion with equal weightings

W2: Fusion with weights from trained + modal

W3: Fusion with weights from trained

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Four Complementary Coefficients

Forbes	Simple Match	Tanimoto	Russell/Rao
$\frac{na}{(a+b)(a+c)}$	$\frac{a+d}{n}$	$\frac{a}{a+b+c}$	$\frac{a}{n}$

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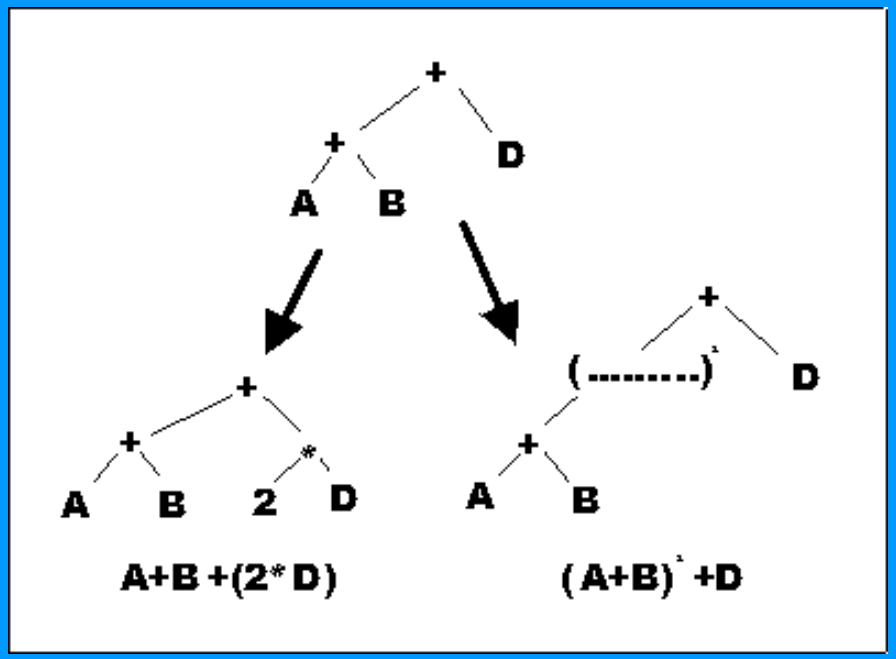
Formula Derivation

Decision tree method



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Formula Derivation

$$\frac{n^{l_1}(\pm i_1 a \pm i_2 b \pm i_3 c \pm i_4 d)^{m_1}(\pm i_5 a \pm i_6 b \pm i_7 c \pm i_8 d)^{m_2}}{n^{l_2}(\pm i_9 a \pm i_{10} b \pm i_{11} c \pm i_{12} d)^{m_3}(\pm i_{13} a \pm i_{14} b \pm i_{15} c \pm i_{16} d)^{m_4}}$$

- Driven by GA
- $l_{1\text{-}2} = 0$ or 1; $i_{1\text{-}16} = 0$, 1, 2 or 3; $m_{1\text{-}4} = 0$, 1 or ½
- Uses a 58 bit bitstring
- Same fitness function & training regime as before
- Tests included to remove erroneous formulae
- May require simplification
- Ranges are difficult to deduce

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Formula Results

Class	Actives	Search Results (top 500)	Tan (top 500)	Best Formula
64220	143075	32	32	(-3a+3b-2d) / (-3b-c)
64220	188743	33	33	
78413	154230	5	6	(-3b+2c+3d) / (b-2c+2d)(-3a-3c-d)
78413	195947	4	4	
12200	186494	4	4	n(-2a)(-3a-3c+d) / (3a-3b-c+2d)(-3a-b-d)
12200	174953	2	4	
80499	197635	3	4	sqrt(c+3d) / (-a-b-c-3d)
80499	257429	4	5	
59210	183938	23	22	(2a-3b+3d)(-3a-b-3c) / (3a)
59210	227061	3	3	

$$\log_{10} \frac{n\left(|ad-bc|-\frac{n}{2}\right)^2}{(a+b)(a+c)(b+d)(c+d)}$$

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Fusion of Pathlengths

- MDDR database characterised by Daylight and BCI fingerprints in sets of different pathlength
- BCI – atom sequences of length 2-3, 4-5, 6-7, 8-9
- Daylight – pathlengths 2-4, 5-7, 8-10, 11-13, 14-16, 17-19, 20-22, 23-25, 26-28, 29-31

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Fusion of Pathlengths

- 20 compounds each from 11 active classes
- Fusion of all possible 2, 3, and 4 sets for BCI
- Fusion of all possible 2 and 3 sets for Daylight

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Daylight Results

Class	Full	Double		Triple	
5HT3 antagonisis	23.60	5-7/20-22	32.63	8-10/17-19/29-31	?
5HT1A agonists	20.88	8-10/26-28	22.45	2-4/8-10/26-28	23.77
5HT reuptake inhibitor	21.81	2-4/5-7	19.68	2-4/5-7/29-31	20.71
D2 antagonists	20.53	2-4/5-7	18.79	2-4/5-7/29-31	18.95
Renin inhibitor	79.23	5-7/8-10	87.77	2-4/5-7/8-10	85.36
Angiotensin II AT1 antagonists	60.63	2-4/5-7	59.45	2-4/5-7/8-10	57.72
Thrombin inhibitor	30.82	2-4/5-7	31.21	2-4/5-7/29-31	29.72
Substance P antagonist	28.09	5-7/8-10	32.54	2-4/5-7/8-10	32.94
HIV protease inhibitor	35.73	2-4/5-7	34.13	2-4/5-7/8-10	33.75
Cyclooxygenase inhibitor	10.10	17-19/20-22 20-22/23-25	12.76	17-19/20-22/23-25	12.98
Protein kinase C inhibitor	31.63	8-10/11-13	22.69	2-4/8-10/11-13	25.38

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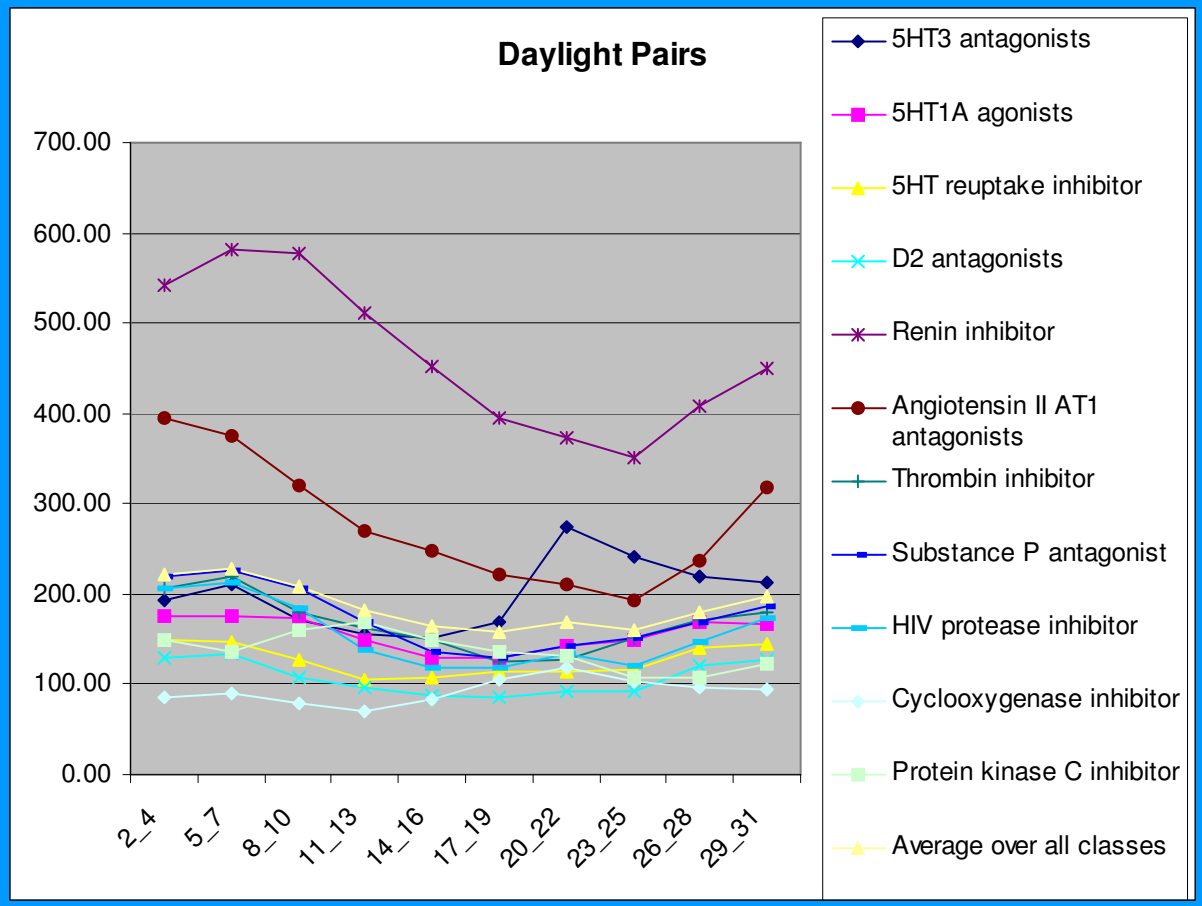
Daylight Pairs - contributions



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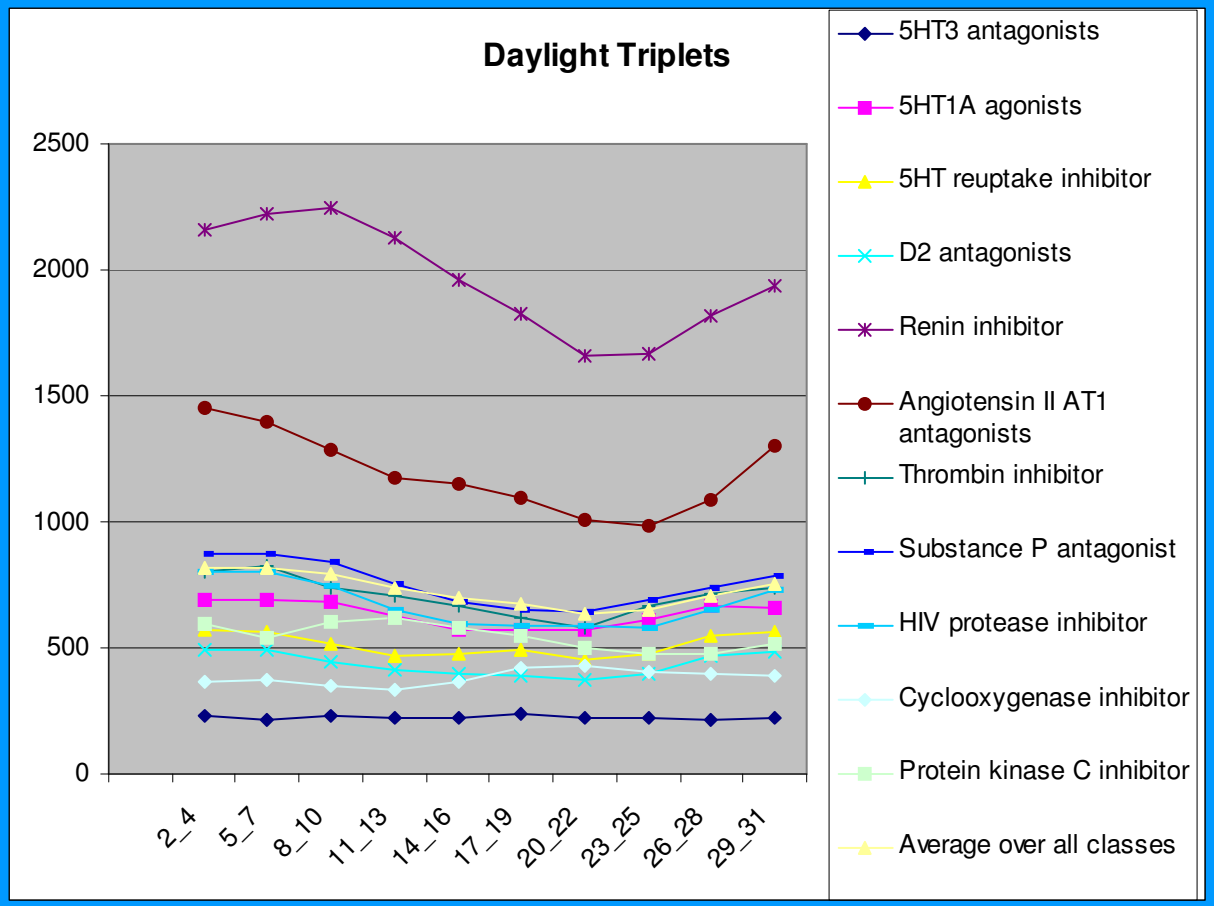
Daylight Triplets - contributors



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K-means clustering

- Non-hierarchical, relocation
- Initial set of k seeds as cluster centre
  - Assign compounds to cluster centre
  - Recalculate cluster centre
  - Repeat until no relocation of compounds

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K-modes clustering

- Uses association coefficient - Tanimoto
- Modes instead of means for clusters
- Frequency based update method
- Need to optimise modal threshold

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Identifying Multiple Classes

- To identify multiple classes and deduce optimum threshold
- 150 classes from MedChem02
- Modal fingerprints for each class generated at 0%, 10%,…,90% threshold
- Ratio of bits set at each threshold to bits set at 0% plotted

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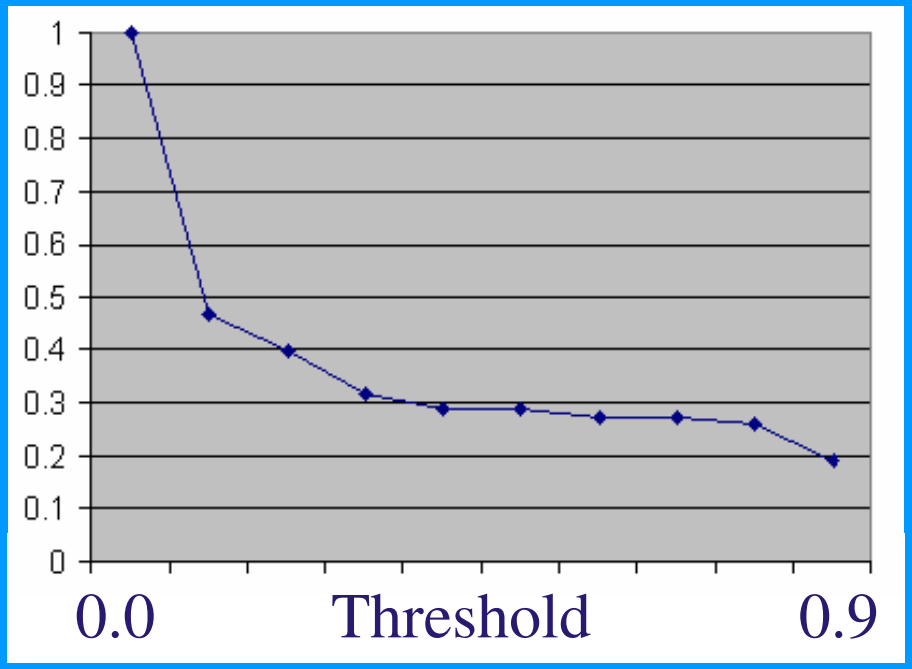
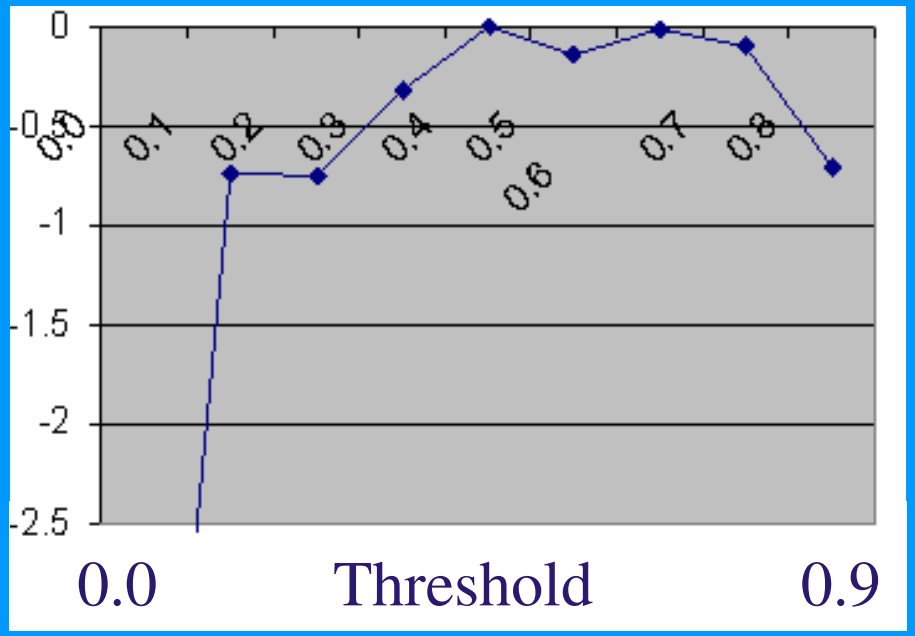
Iron Chelator – 42 analogues



Bits at threshold vrs Bits at 0%



First derivative
Shows two peaks indicating two classes

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Using class seeds to cluster

- 150 classes form MedChem02 database
- Modal fingerprint generated for each class
- Used as seeds for k-modes algorithm
- Also used random seeds
- Repeated using 300 and using no relocation
- No improvement in cluster performance
- Repeated again using 250, 500, 1K, 2K, 4K random seeds
  - Considerable improvement observed

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Summary

- Methods for improving searches are possible
- Class-based methods
  - Weighted fusion of coefficients
  - Tailored coefficients
  - Different pathlengths
- Use of modal fingerprint

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