



Volgograd State Medical University
Pharmacology Department

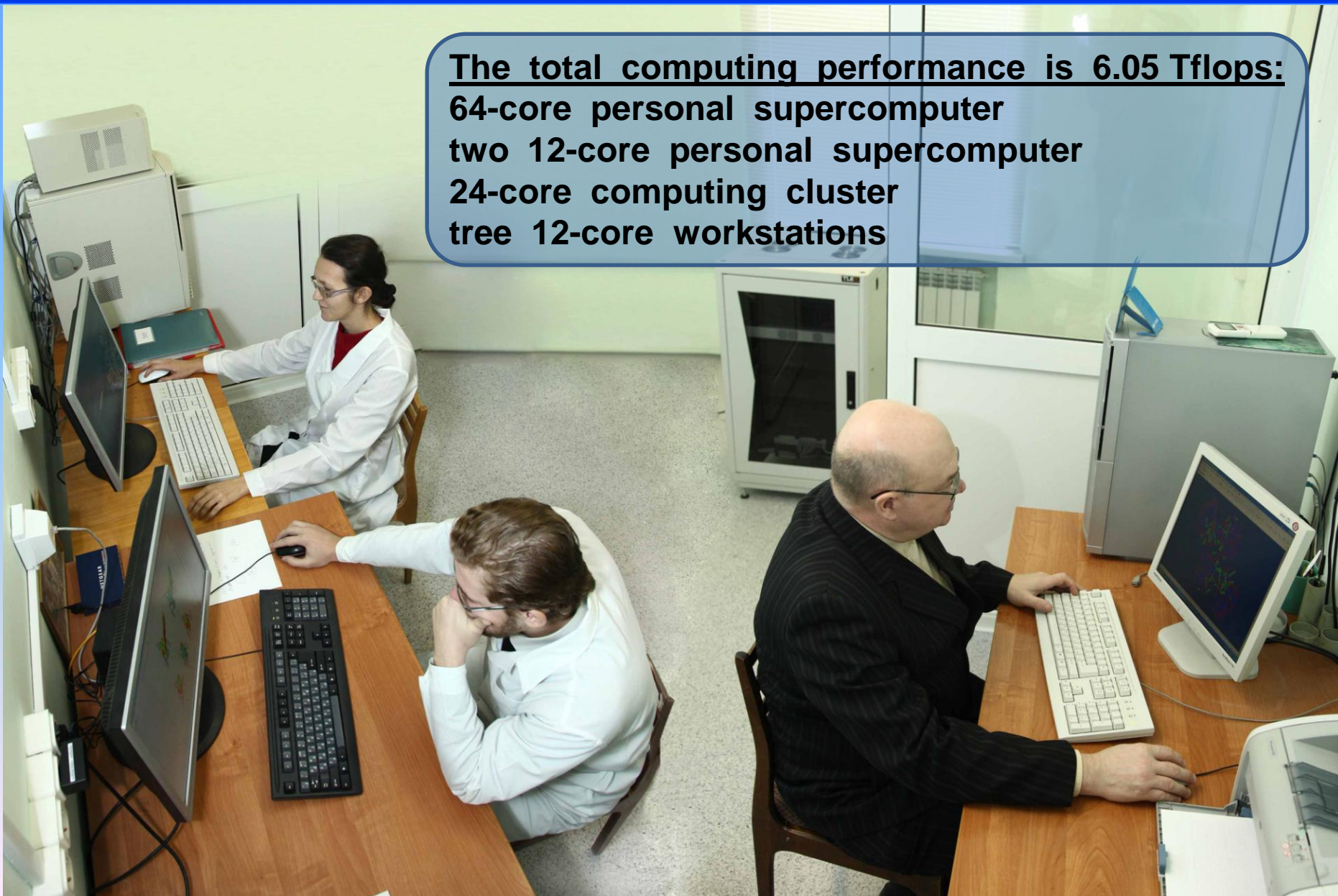


Consensus Emsemble
Neural Network Modeling
Maillard Reaction Inhibitors

Pavel M. Vassiliev

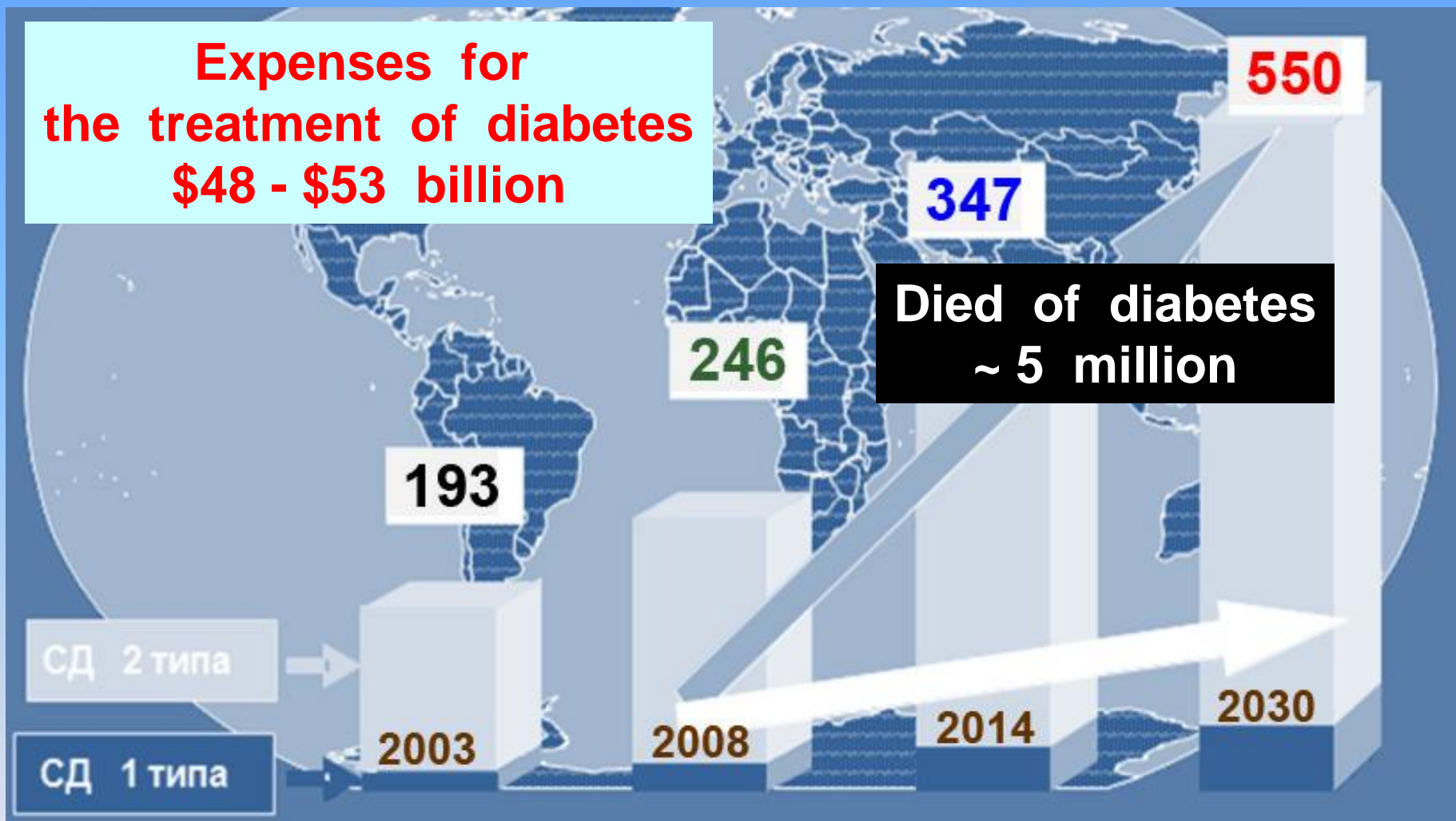
Laboratory of molecular modeling and computer search for drug substances

The total computing performance is 6.05 Tflops:
64-core personal supercomputer
two 12-core personal supercomputer
24-core computing cluster
tree 12-core workstations



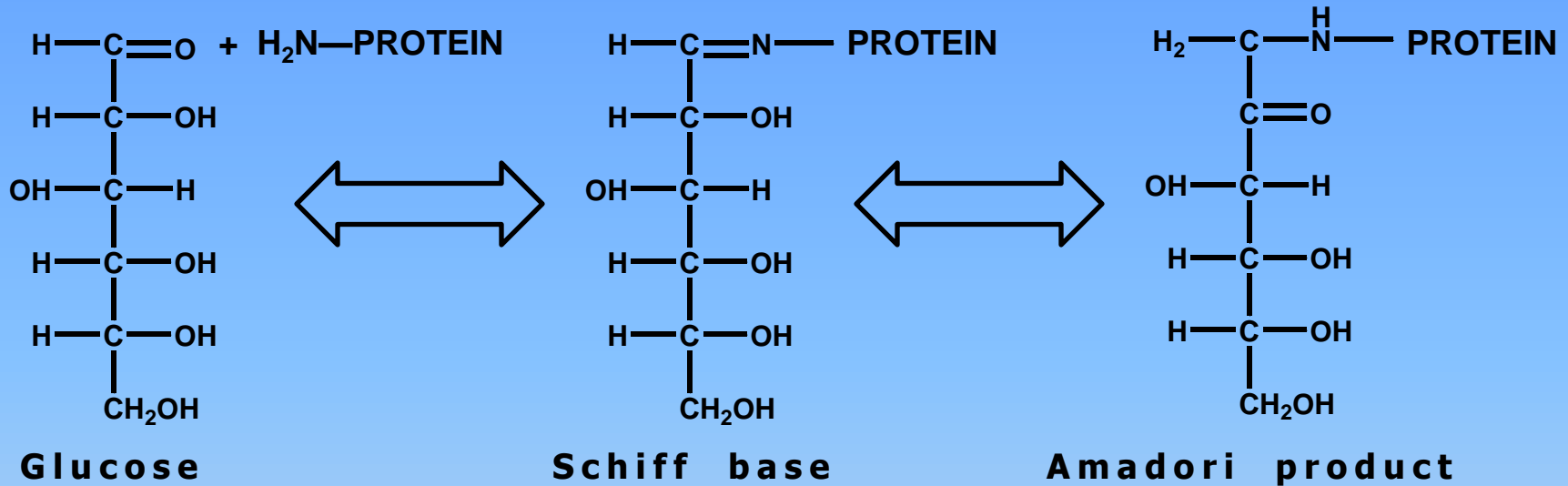
The incidence of diabetes mellitus

**Expenses for
the treatment of diabetes
\$48 - \$53 billion**



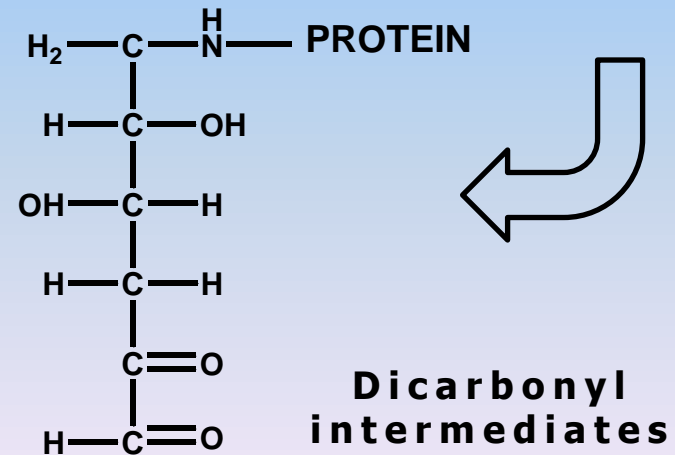
**Russia 2013: 4.0 million registered patients;
12.5 million by ADF estimate.**

The main stages of the Maillard reaction



AGE—PROTEIN
and / or
PROTEIN—AGE—PROTEIN

**Advanced Glycation
 End products (AGEs)**



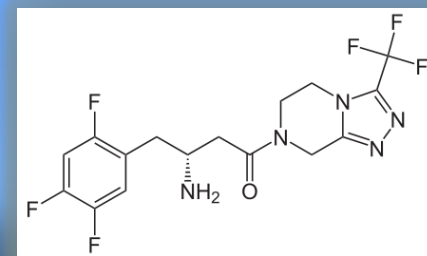
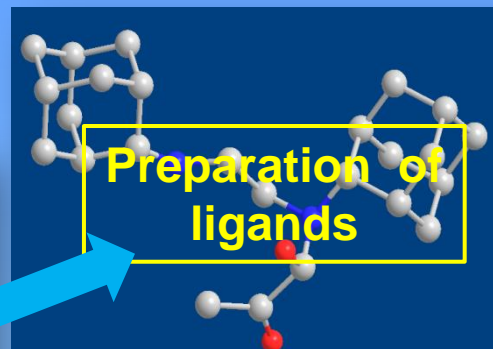
Workflow of consensus searching

Tested Substances v01 05 February 2016

Structure

Creation of focused library

Mol_ID	Code	Brutto formula	Mol weight
44	AZH-0100	C ₁₈ H ₂₁ N ₃	279.3



ИТ "Микрокосм" - прогноз свойств органических соединений

QSAR calculation

Расчет коэффициентов сходства Танимото цветковых структур к эталонным структурам по QL2-дескрипторам

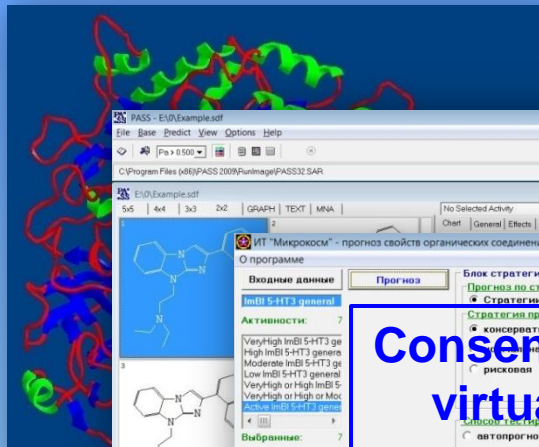
Эталонные структуры: MRI Standards
Тестовые структуры: FLib v00

Вывод: FLib v00 MRI TestSim.bt

Расчитать коэффициенты сходства

Target validation

Workflow of consensus searching



ИТ "Микрокосм" - прогноз свойств органических соединений

Входные данные: ImBI 5-HT3 agonist

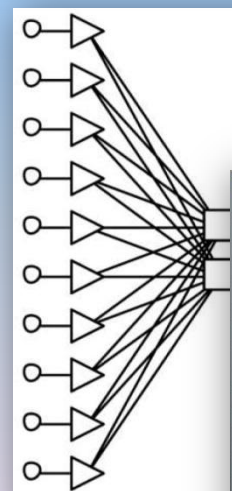
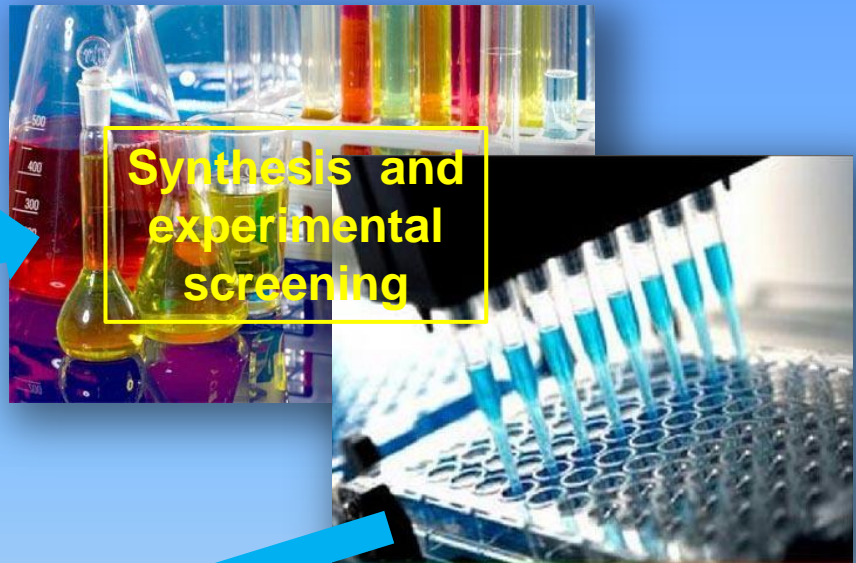
Активности: VeryHigh ImBI 5-HT3 ge, High ImBI 5-HT3 general, Moderate ImBI 5-HT3 ge, Low ImBI 5-HT3 general, VeryHigh or High ImBI 5-HT3 ge, VeryHigh or High or Mod. Active ImBI 5-HT3 ge

Выбранные: Moderate ImBI 5-HT, Low ImBI 5-HT3 ge, VeryHigh or High ImBI 5-HT3 ge, Active ImBI 5-HT3 ge

Текущее состояние: Автопрогноз по методу Ближайшего соседа

Fo = 62.66 185 Fn = 56.72

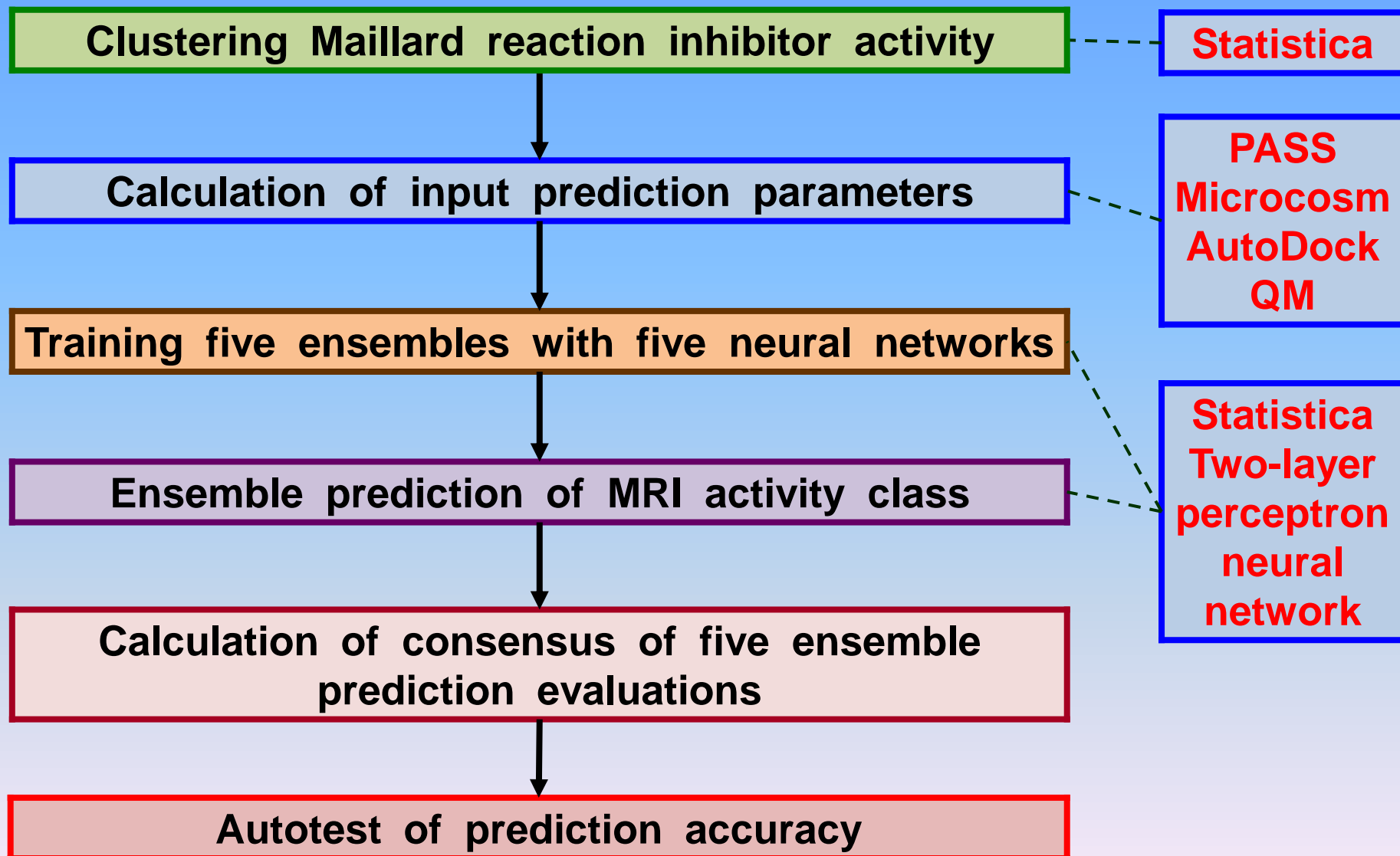
Consensus virtual screening



Neural network QSAR modeling

Chemical ID	Level	Level_h	Level_l	Level_m	PASS_DPP4_PASS_DPP4	TSim_DPP4	Docq_DPP4	PASS_PPARG_PASS_PPARG	TSim_PPARG	Docq_PPARG	PASS_PVGLP		
HC-004	high	high	high	high	0.01	0.11	0.1415	-8.10	0.03	0.00	0.2257	-6.29	0.06
KC-C	high	high	high	high	0.01	0.02	0.1903	-8.86	0.00	0.00	0.2093	-8.86	0.00
S-0051a	high	high	high	high	0.01	0.02	0.1903	-11.58	0.02	0.01	0.2038	-11.58	0.02
HC-009	high	high	high	high	0.00	0.00	0.1944	-6.09	0.00	0.00	0.1944	-6.09	0.00
BUMZ-0010	high	high	high	high	0.01	0.01	0.1944	-5.69	0.00	0.00	0.1944	-5.69	0.00
AB-0052	high	high	high	high	0.01	0.02	0.2002	-7.13	0.02	0.01	0.2002	-7.13	0.02
RUS-0211	high	high	high	high	0.00	0.00	0.1148	-6.36	0.00	0.00	0.1148	-6.36	0.00
IS-0201	high	high	high	high	0.00	0.00	0.1198	-6.30	0.00	0.00	0.1198	-6.30	0.00
AB-0053	high	high	high	high	0.01	0.02	0.2003	-7.21	0.00	0.00	0.2003	-7.21	0.00
AB-0045	high	high	high	high	0.01	0.01	0.2203	-7.34	0.00	0.00	0.2203	-7.34	0.00
AB-0051	high	high	high	high	0.01	0.01	0.1994	-7.06	0.01	0.00	0.1994	-7.06	0.01
PV-0174	high	high	high	high	0.00	0.00	0.1837	-7.88	0.00	0.00	0.1837	-7.88	0.00
LOEIP-0002	high	high	high	high	0.00	0.00	0.1600	-9.52	0.01	0.00	0.1600	-9.52	0.01
HC-0018	high	high	high	high	0.00	0.00	0.1600	-9.49	0.00	0.00	0.1600	-9.49	0.00
KC-B	high	high	high	high	0.00	0.00	0.1600	-6.45	0.00	0.00	0.1600	-6.45	0.00
IS-0255	high	high	high	high	0.00	0.00	0.1600	-7.89	0.02	0.00	0.1600	-7.89	0.02
AB-0019	high	high	high	high	0.00	0.00	0.1600	-7.30	0.00	0.00	0.1600	-7.30	0.00
KC-A	high	high	high	high	0.00	0.00	0.1600	-6.91	0.00	0.00	0.1600	-6.91	0.00
A2H-0140	high	high	high	high	0.01	0.01	0.2068	-9.89	0.00	0.00	0.2068	-9.89	0.00
RUI-0011	high	high	high	high	0.00	0.00	0.1987	-7.88	0.00	0.00	0.1987	-7.88	0.00
KC-C	high	high	high	high	0.01	0.01	0.2054	-7.33	0.01	0.00	0.2054	-7.33	0.01
AB-0021	high	high	high	high	0.01	0.01	0.2180	-7.32	0.00	0.00	0.2180	-7.32	0.00
AB-0058	high	high	high	high	0.04	0.04	0.2292	-7.22	0.01	0.00	0.2292	-7.22	0.01
AB-0059	high	high	high	high	0.01	0.01	0.2195	-7.72	0.06	0.00	0.2195	-7.72	0.06
KC-D	high	high	high	high	0.00	0.00	0.2058	-8.54	0.00	0.00	0.2058	-8.54	0.00
KC-F	high	high	high	high	0.03	0.07	0.1644	-8.46	0.00	0.00	0.1601	-6.48	0.00
RUI-0033	high	high	high	high	0.01	0.02	0.1788	-7.33	0.00	0.00	0.1607	-7.85	0.00
RUI-0012	high	high	high	high	0.02	0.03	0.1850	-7.09	0.01	0.00	0.1607	-7.81	0.01
RAI-0004	high	high	high	high	0.01	0.03	0.1216	-7.49	0.01	0.00	0.1744	-8.16	0.00
TKNS-0003	high	high	high	high	0.05	0.08	0.1660	-8.83	0.01	0.01	0.1652	-10.11	0.01
KC-0718a	high	high	high	high	0.10	0.08	0.1830	-7.71	0.00	0.00	0.1898	-7.82	0.00
KC-0646a	high	high	high	high	0.37	0.47	0.1605	-6.34	0.00	0.00	0.1604	-7.03	0.01

Workflow of consensus ensemble neural network modeling

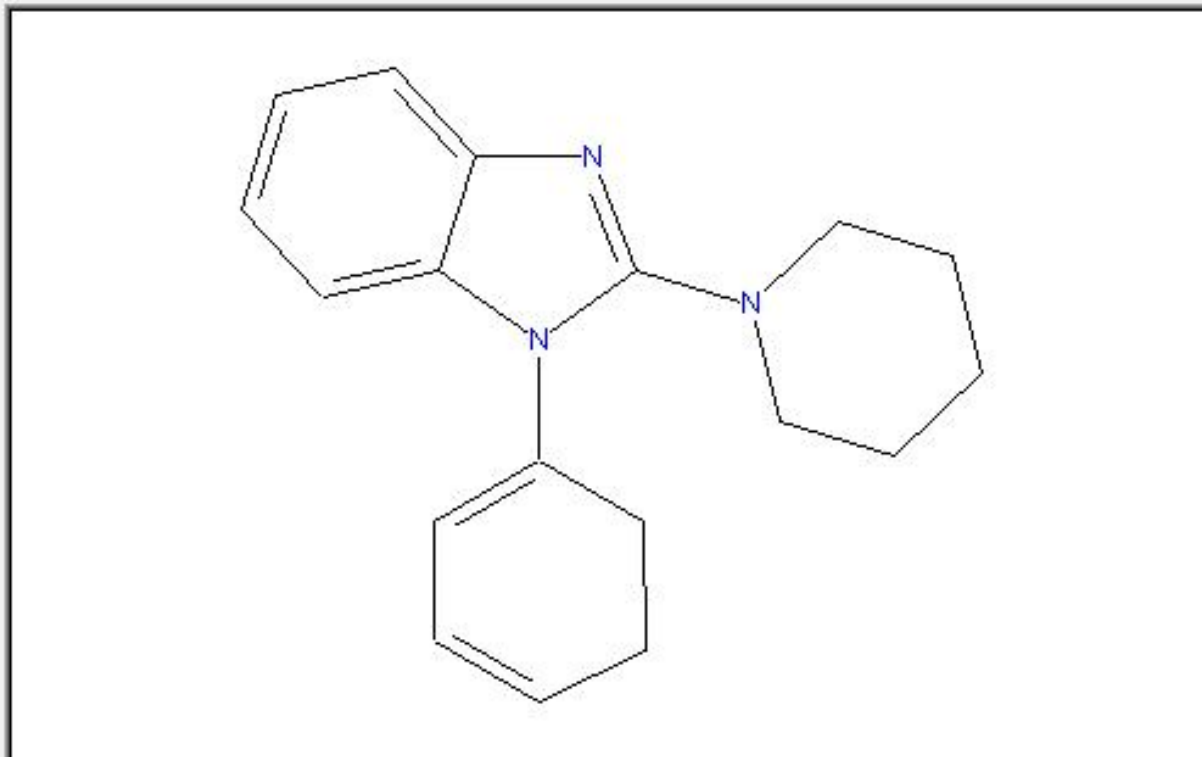


Focused library

Tested Substances v01

05 February 2016

Structure



Mol_ID

44

Code

AZH-0100

Brutto formula

C₁₈H₂₁N₃

Mol weight

279.3

2059 structures

PASS system

The screenshot displays the PASS system interface. The main window shows four chemical structures (1, 2, 3, 4) in a 2x2 grid. Structure 1 is highlighted in blue. The interface includes a menu bar (File, Base, Predict, View, Options, Help), a toolbar with a filter set to $P_a > 0.500$, and a file path: `C:\Program Files (x86)\PASS 2009\RunImage\PASS32.SAR`. A secondary window titled "E:\0\Example.sdf" shows a heatmap of activity predictions. The heatmap has a legend at the top with "No Selected Activity" and tabs for "Chart", "General", "Effects", "Mechanisms", "Toxicity", and "Metabolism". Below the heatmap, the following statistics are displayed:

- 32 Substructure Descriptors; 0 new.
- There are 3 known activities.
- Drug-Likeness: 0.931
- 56 of 3750 Possible Activities
- 8 of 418 Possible Pharmacological Effects
- 45 of 3032 Possible Molecular Mechanisms
- 3 of 58 Possible Side Effects and Toxicity
- 0 of 196 Possible Metabolism-Related Actions
- 0 of 11 Possible Gene Expression Regulation
- 0 of 35 Possible Transporters-Related Actions

1/4

*P_a/P_i — ratio of probabilities
for activity and inactivity*

Information Technology «Microcosm»

Анализ сходства к эталонам

Расчет коэффициентов сходства Танимото тестовых структур к эталонным структурам по QL2-дескрипторам

Эталонные структуры MRI Standards

Тестовые структуры FLib v00

Вывод:

- общие средние**
- средние для каждого из эталонов**
- лучшие по сходству к эталонам----->**
- полные таблицы сходства**

Вывод в файл:

FLib v00 MRI TestSim.txt

Сколько лучших выводить:

3

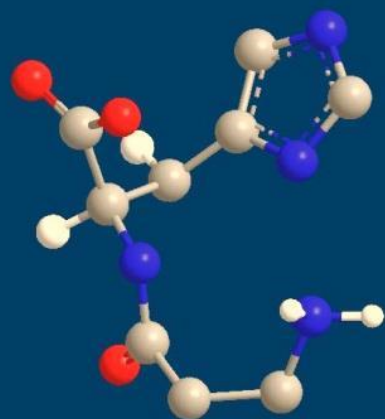
Расчитать коэффициенты сходства

T_{QL} – QL-modified Tanimoto similarity coefficient

Quantum-chemical QSAR-modeling

Aminoguanidine

MOPAC-2012 PM7



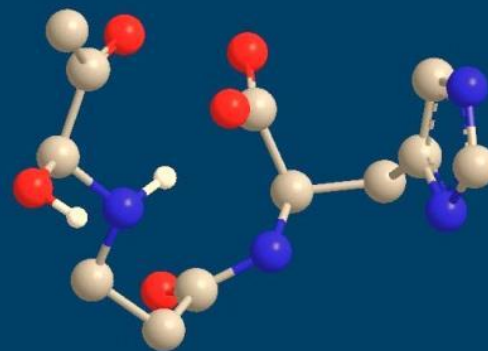
$\Delta G = -2925.99$

+



$\Delta G = -1012.57$

$\Delta G = -0.68 \text{ eV}$



$\Delta G = -3939.24$

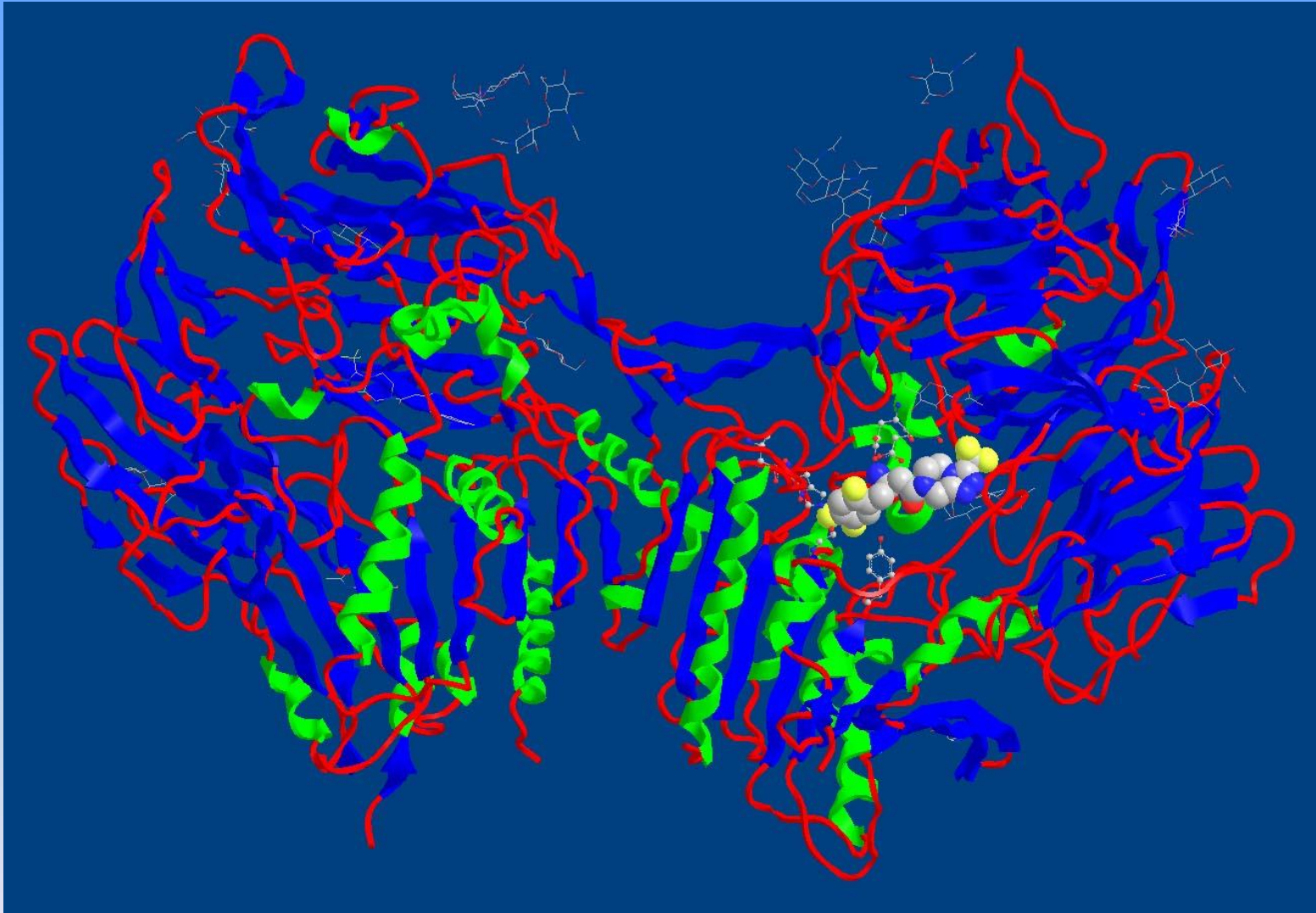
$$\text{Act} = 44.540 + 60.168 \cdot \Delta G - 12.601 \cdot \Delta E_{\text{HOMO}}$$

$0.00157 \qquad \qquad \qquad 0.0237$

N=10 R=0.911 s=4.11 F_{2,7}=17.0 p=0.0021

Act = relative activity to reference

AutoDock Vina



ΔE — *docking energy*

Clustering MRI activity

Clustering MRI(10-3) v01.stw*

- Cluster Analysis (DD MRI(10-3) v01)
 - K-means clustering results dialog**
 - Cluster Means (DD MRI(10-3) v01)
 - Euclidean Distances between Clusters (DD MRI(10-3) v01)
 - Analysis of Variance (DD MRI(10-3) v01)
 - Plot of Means for Each Cluster
 - Descriptive Statistics for Cluster 1 (DD MRI(10-3) v01)
 - Descriptive Statistics for Cluster 2 (DD MRI(10-3) v01)
 - Descriptive Statistics for Cluster 3 (DD MRI(10-3) v01)
 - Members of Cluster Number 1 (DD MRI(10-3) v01)
 - Members of Cluster Number 2 (DD MRI(10-3) v01)
 - Members of Cluster Number 3 (DD MRI(10-3) v01)

Variable	Cluster Means (DD MRI(10-3) v01)		
	Cluster No. 1	Cluster No. 2	Cluster No. 3
D(10 ⁻³)%	78.91594	39.33603	13.70664

Cluster Number	Euclidean Distances between Clusters		
	Distances below diagonal		
	Squared distances above diagonal		
	No. 1	No. 2	No. 3
No. 1	0.00000	1566.569	4252.252
No. 2	39.57991	0.000	656.866
No. 3	65.20930	25.629	0.000

K-means method

Levels of MRI activity

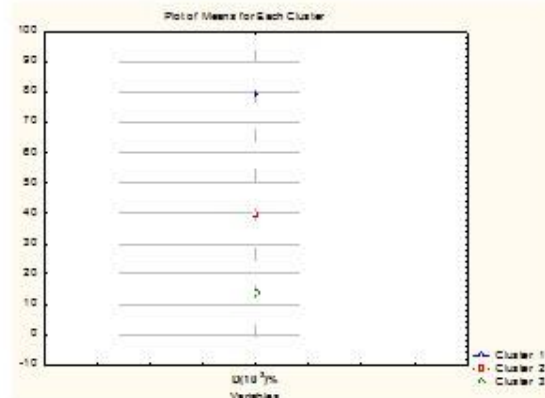
h(10⁻³) — Δ(10⁻³) > 58.4 %

hm(10⁻³) — Δ(10⁻³) > 26.4 %

h(10⁻⁴) — Δ(10⁻⁴) > 35.5 %

hm(10⁻⁴) — Δ(10⁻⁴) > 14.3 %

Variable	Between Clusters		Within Clusters		F
	SS	df	SS	df	
D(10 ⁻³)%	177341.8	2	19592.27	243	1099.77



Variable	Descriptive Statistics for Cluster 1 (DD Cluster contains 64 cases)		
	Mean	Standard Deviation	Variance
D(10 ⁻³)%	78.91594	11.40821	132.2088

Variable	Descriptive Statistics for Cluster 2 (DD Cluster contains 63 cases)		
	Mean	Standard Deviation	Variance
D(10 ⁻³)%	39.33603	0.820171	0.672666

K-means clustering results dialog

280 substances

Prediction parameters for Neural Network

DPP-4 – dipeptidyl peptidase 4 inhibitors

PASS, Microcosm, AutoDock; 4 variables

PPAR γ – PPAR gamma activators

PASS, Microcosm, AutoDock; 4 variables

PYGL – glycogen phosphorylase inhibitors, 4 sites

PASS, Microcosm, AutoDock; 10 variables

MRI – Maillard reaction inhibitors

PASS, Microcosm, QM; 3 variables

Prediction parameters for Neural Network

CLB – cross-link breakers

PASS, Microcosm; 4 variables

MGAM – alpha glucosidase inhibitors, 2 sites

PASS, Microcosm, AutoDock; 7 variables

GK – glucokinase activators

PASS, Microcosm, AutoDock; 3 variables

***Total 35 variables
as neuron input signals***

Training neural networks

The screenshot displays the Statistica 7.2 interface. A data table titled 'Data for Network' is visible, with columns for various input and output variables. A dialog box for 'Active neural networks' is open, showing a table with columns for 'Net', 'Net name', 'Training', 'Test', 'Algorit.', 'Errorfu.', 'Hidden', and 'Output'. A 'Neural network training in progress...' window is also open, displaying the following information:

Building network 3 (MLP 35-21-2, tanh, tanh)
Cycle=45:
Classification rate: Train=93.5484, Test=80.3279

The background data table contains the following data:

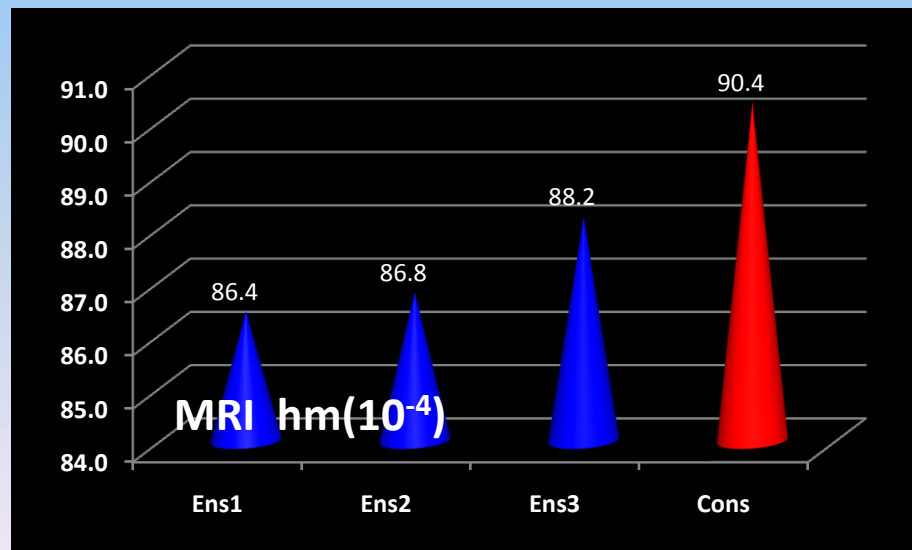
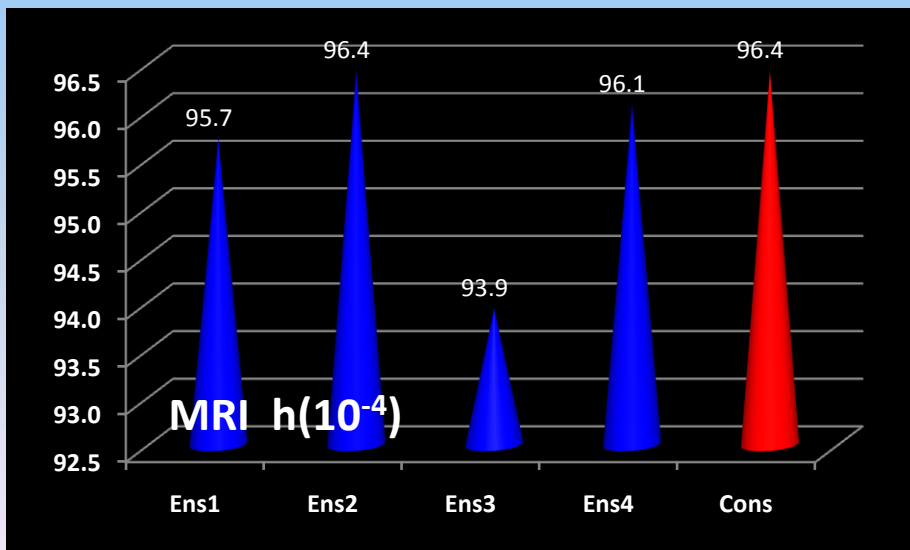
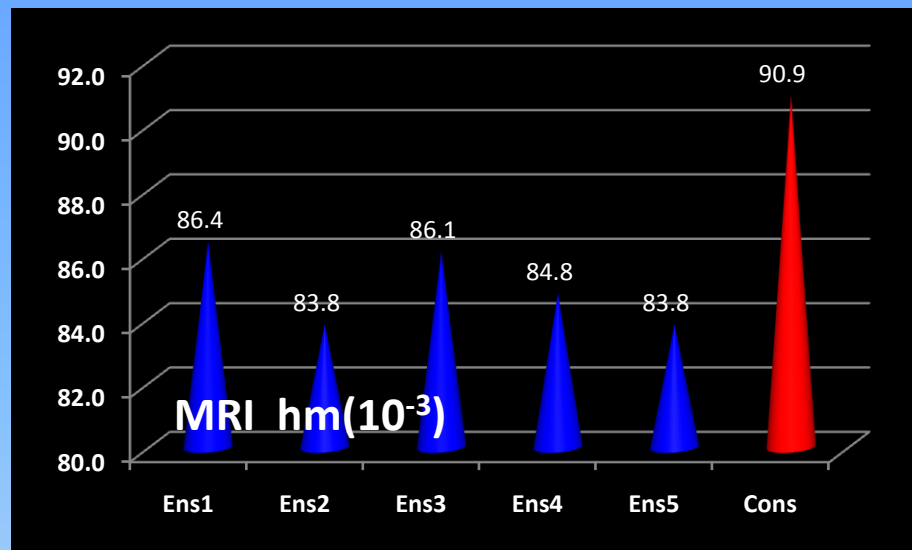
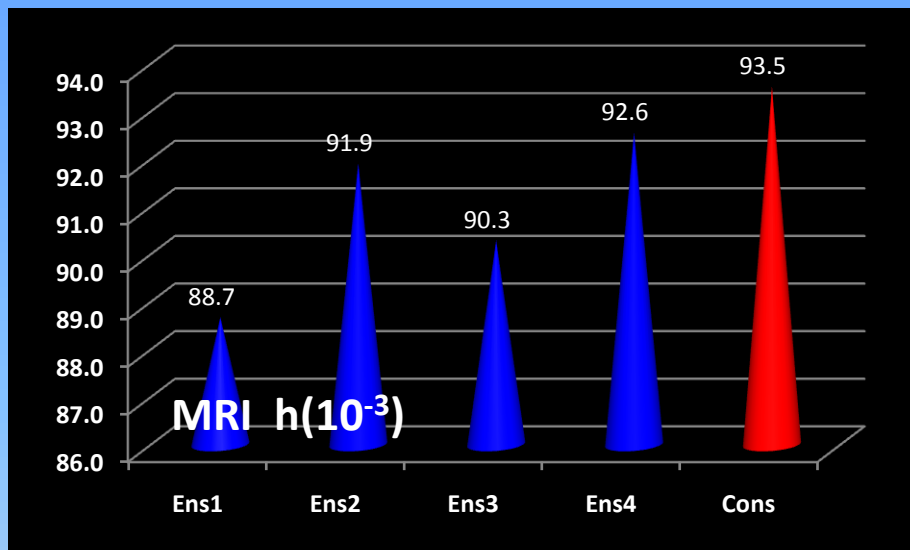
	1	2	3	4	5	6	7	8	9	10	11	12	13
	D(10-3)	Level0	Level_h	Level_hm	PASS_DPP4	PASS_DPP	TSim_DPP4	Dock_DPP4	PASS_PPARG	PASS_PPARG	TSim_PPARG	Dock_PPARG	PASS_PYGLP
HC-0054	97.36	high	high	hm	0.01	0.11	0.1415	-8.18	0.03	0.06	0.2257	-8.29	0.06
KC-G	97.20									0.00	0.2093	-8.86	0.00
S-0051a	94.97									0.01	0.2038	-11.58	0.02
HC-0009	94.51									0.00	0.1544	-8.09	0.00
BUIMZ-0010	93.25									0.01	0.1271	-5.69	0.00
AB-0052	93.01									0.01	0.2002	-7.13	0.02
RUS-0217	92.90									0.00	0.1148	-6.36	0.00
IS-0201	91.68									0.00	0.1198	-6.30	0.00
AB-0053	91.57									0.00	0.2003	-7.21	0.00
AB-0045	91.10									0.01	0.2263	-7.34	0.00
AB-0051	91.07									0.01	0.1994	-7.06	0.01
FV-0174	90.71									0.00	0.1837	-7.88	0.00
LOSLP-0002	90.50									0.00	0.1880	-9.52	0.01
HC-0018	89.90									0.00	0.1653	-9.46	0.00
KC-B	89.74									0.1505	-6.45	0.00	
IS-0255	89.26									0.2213	-7.89	0.02	
AB-0019	88.76									0.2222	-7.30	0.00	
KC-A	87.59									0.1629	-6.91	0.00	
AZH-0140	87.33									0.2068	-9.89	0.00	
RUI-0011	86.99									0.00	0.1967	-7.68	0.00
KC-C	86.65									0.01	0.2054	-7.33	0.01
AB-0021	86.48									0.01	0.2180	-7.32	0.00
AB-0058	86.45									0.04	0.2292	-7.22	0.01
AB-0059	86.41									0.01	0.2195	-7.72	0.06
KC-D	86.13	high	high	hm	0.01	0.01	0.1752	-8.44	0.00	0.00	0.2058	-8.54	0.00
KC-P	85.97	high	high	hm	0.03	0.07	0.1644	-6.46	0.00	0.00	0.1601	-6.48	0.00
RUI-0033	84.09	high	high	hm	0.01	0.02	0.1788	-7.33	0.00	0.00	0.1907	-7.85	0.00
RUI-0012	84.07	high	high	hm	0.02	0.03	0.1850	-7.09	0.01	0.00	0.1987	-7.61	0.00
RAI-0004	83.99	high	high	hm	0.01	0.03	0.1216	-7.49	0.01	0.00	0.1744	-8.16	0.00
TONS-0508	82.19	high	high	hm	0.35	0.98	0.1993	-8.93	0.01	0.01	0.1852	-10.11	0.01
KC-0718a	82.11	high	high	hm	0.10	0.08	0.1630	-7.71	0.00	0.00	0.1898	-7.82	0.00
KC-0646a	82.05	high	high	hm	0.37	0.47	0.1585	-6.34	0.00	0.00	0.1684	-7.03	0.01

Five ensembles with five neural networks

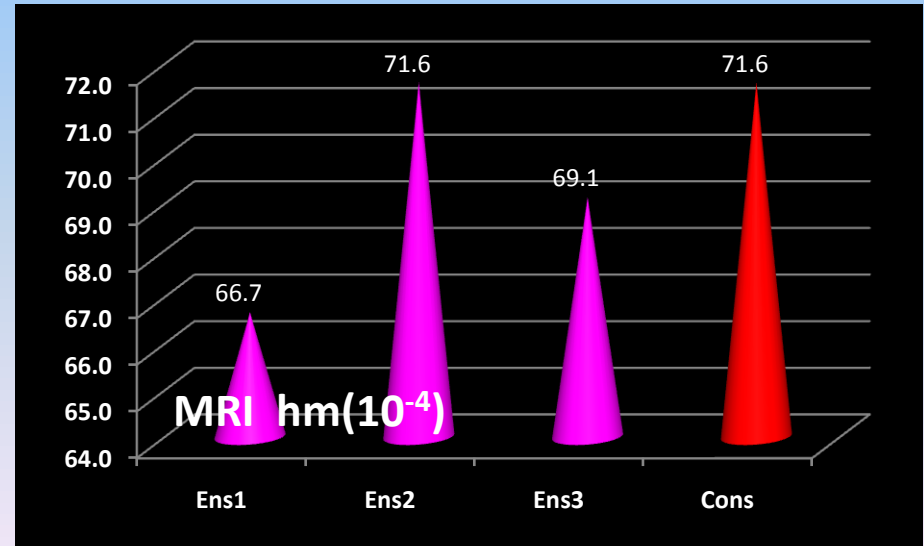
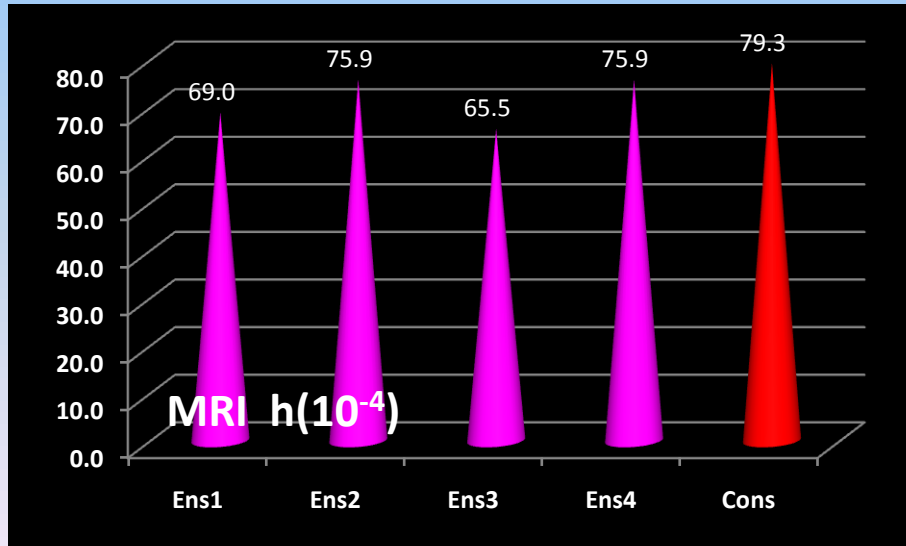
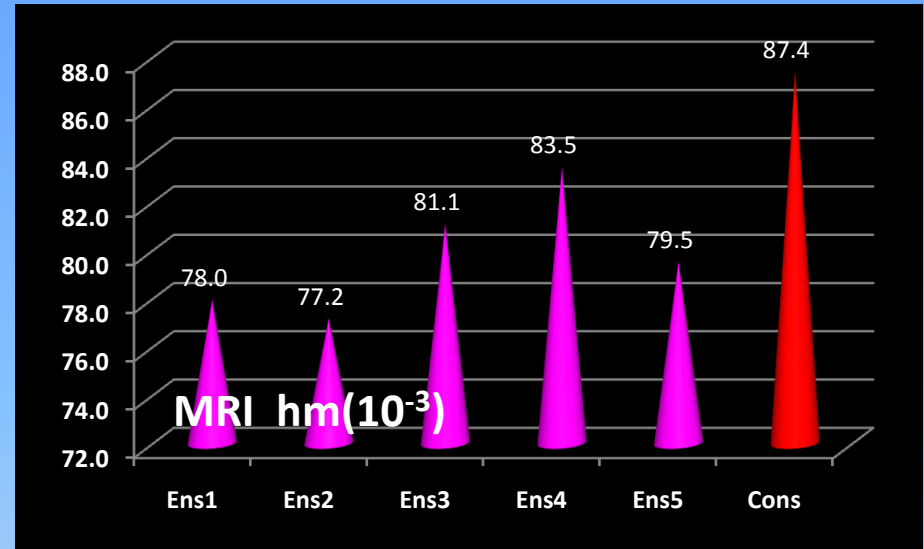
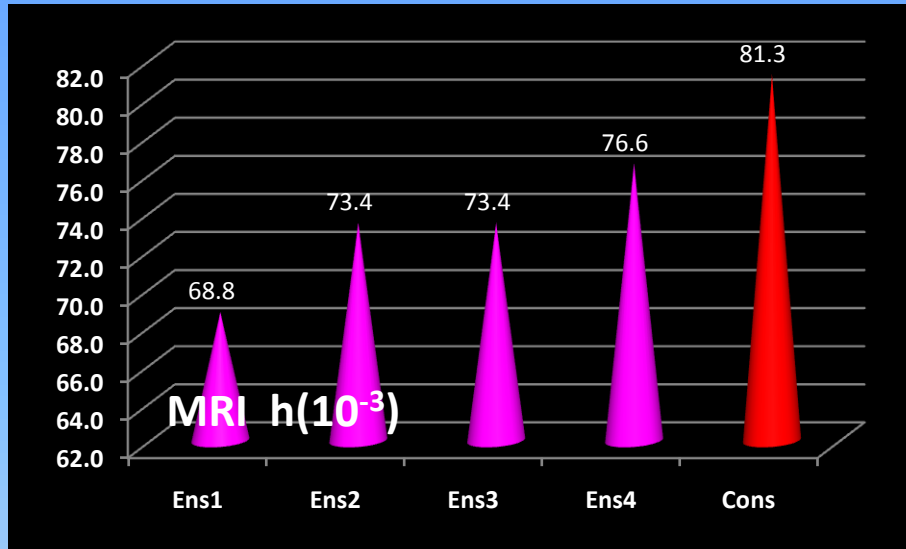
Consensus ensemble neural network prediction

Code	D(10-3) %	Level Initial	Ensemble 1		Ensemble 2		Ensemble 3		Ensemble 4		Ensemble 5		Consensus
			Class	Conf	Class	Conf	Class	Conf	Class	Conf	Class	Conf	Pred
HC-0054	97.36	hm	hm	0.704	inact	0.691	inact	0.642	hm	0.684	hm	0.728	hm
KC-G	97.20	hm	hm	0.728	hm	0.612	hm	0.601	hm	0.680	hm	0.731	hm
S-0051a	94.97	hm	hm	0.718	hm	0.687	hm	0.724	inact	0.746	hm	0.554	hm
HC-0009	94.51	hm	hm	0.724	hm	0.643	hm	0.679	hm	0.730	hm	0.731	hm
BUIMZ-0010	93.25	hm	inact	0.725	inact	0.688	hm	0.636	hm	0.615	hm	0.714	hm
AB-0052	93.01	hm	hm	0.730	hm	0.655	hm	0.715	hm	0.736	hm	0.731	hm
RUS-0217	92.90	hm	hm	0.698	hm	0.651	hm	0.518	inact	0.609	hm	0.688	hm
IS-0201	91.68	hm	hm	0.731	hm	0.735	hm	0.736	hm	0.631	hm	0.731	hm
AB-0053	91.57	hm	hm	0.731	hm	0.722	hm	0.735	hm	0.772	hm	0.731	hm
AB-0045	91.10	hm	hm	0.728	hm	0.556	hm	0.577	hm	0.582	hm	0.717	hm
AB-0051	91.07	hm	hm	0.730	hm	0.687	hm	0.729	hm	0.741	hm	0.731	hm
FV-0174	90.71	hm	hm	0.730	hm	0.571	hm	0.571	hm	0.595	hm	0.731	hm
LOSLP-0002	90.50	hm	hm	0.729	hm	0.654	hm	0.680	hm	0.528	hm	0.722	hm
HC-0018	89.90	hm	hm	0.638	hm	0.683	hm	0.658	hm	0.703	hm	0.685	hm
KC-B	89.74	hm	hm	0.728	hm	0.655	hm	0.660	hm	0.637	hm	0.720	hm
IS-0255	89.26	hm	hm	0.714	hm	0.635	hm	0.654	hm	0.709	hm	0.729	hm
AB-0019	88.76	hm	hm	0.729	hm	0.603	hm	0.644	hm	0.674	hm	0.730	hm
KC-A	87.59	hm	hm	0.731	hm	0.696	hm	0.725	hm	0.705	hm	0.731	hm
AZH-0140	87.33	hm	inact	0.710	inact	0.521	hm	0.586	inact	0.605	inact	0.730	inact
RUI-0011	86.99	hm	hm	0.612	hm	0.578	hm	0.669	hm	0.568	hm	0.695	hm
KC-C	86.65	hm	hm	0.721	hm	0.555	hm	0.594	hm	0.619	hm	0.728	hm
AB-0021	86.48	hm	hm	0.721	hm	0.589	hm	0.629	hm	0.654	hm	0.727	hm
AB-0058	86.45	hm	hm	0.729	hm	0.589	hm	0.630	hm	0.613	hm	0.723	hm
AB-0059	86.41	hm	hm	0.714	hm	0.594	hm	0.653	hm	0.692	hm	0.715	hm
KC-D	86.13	hm	hm	0.730	hm	0.636	hm	0.672	hm	0.649	hm	0.731	hm
KC-P	85.97	hm	hm	0.730	hm	0.676	hm	0.684	hm	0.653	hm	0.718	hm
RUI-0033	84.09	hm	hm	0.705	hm	0.549	inact	0.713	inact	0.601	hm	0.713	hm
RUI-0012	84.07	hm	hm	0.692	hm	0.598	hm	0.686	hm	0.605	hm	0.729	hm
RAI-0004	83.99	hm	inact	0.526	hm	0.689	hm	0.729	hm	0.723	inact	0.538	hm
TONS-0509	82.19	hm	inact	0.729	inact	0.661	hm	0.546	hm	0.580	hm	0.536	hm
KC-0718a	82.11	hm	hm	0.725	hm	0.609	hm	0.622	hm	0.605	hm	0.724	hm
KC-0646a	82.05	hm	hm	0.729	hm	0.663	hm	0.706	hm	0.745	hm	0.707	hm

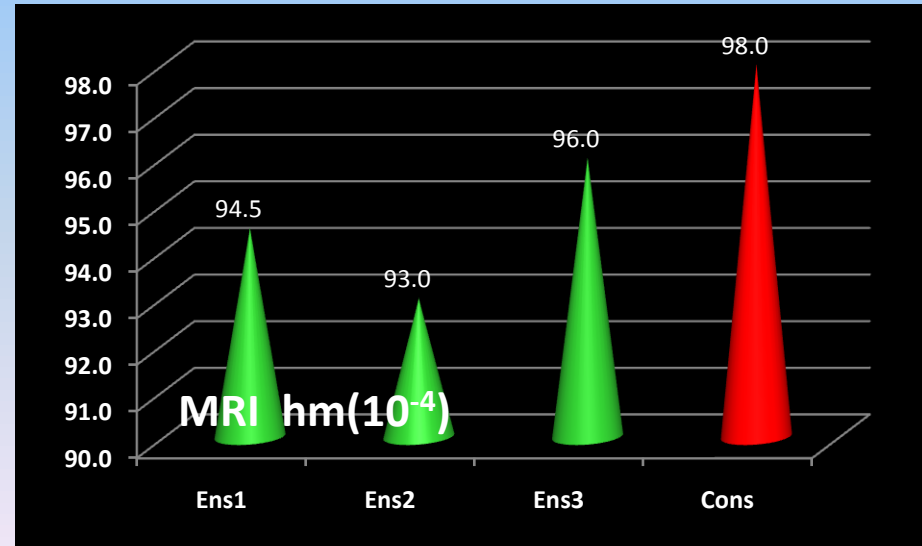
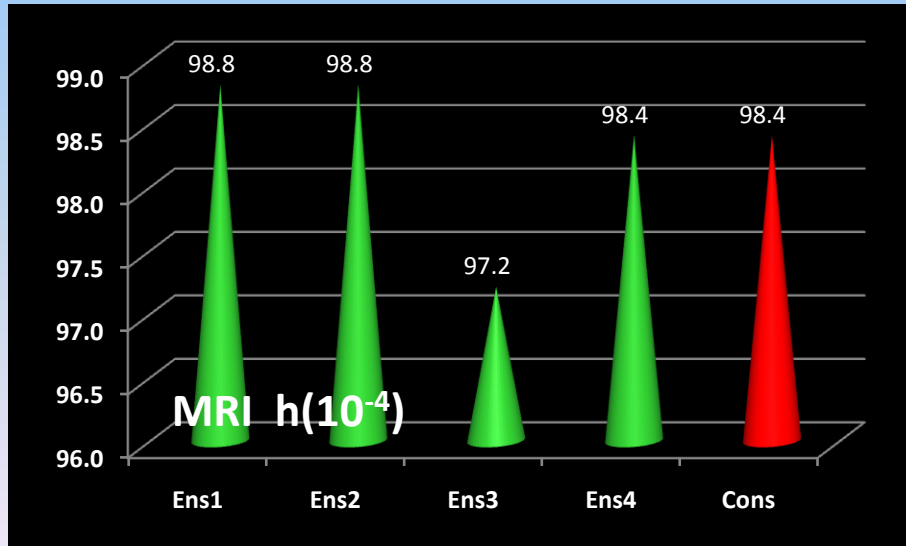
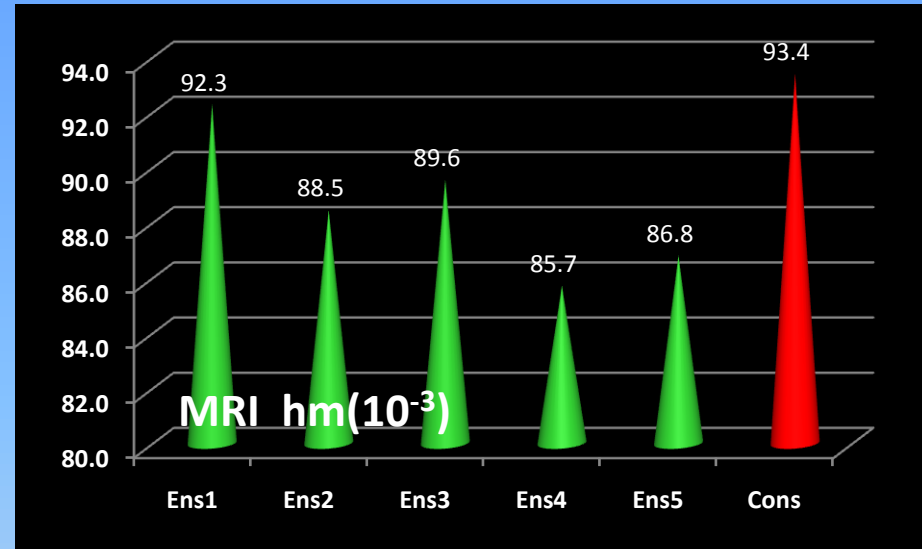
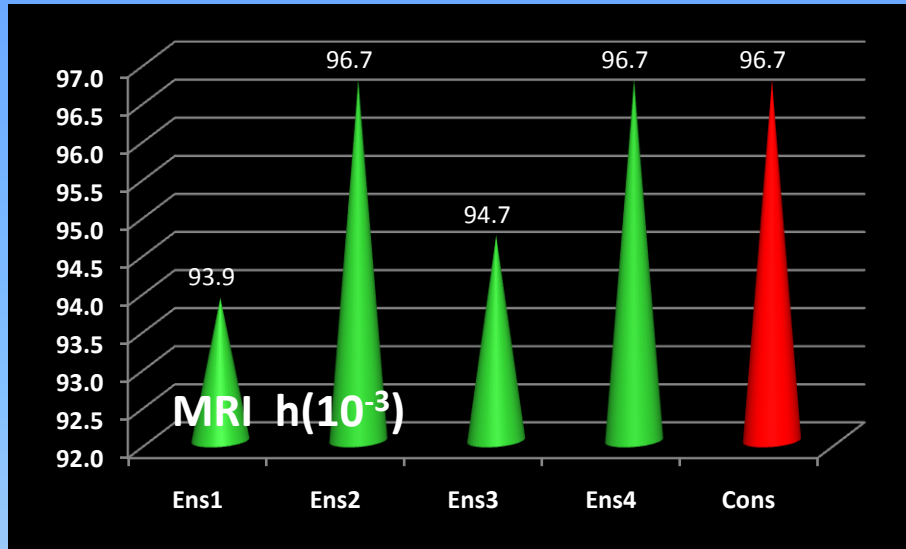
Accuracy Fo of consensus ensemble prediction



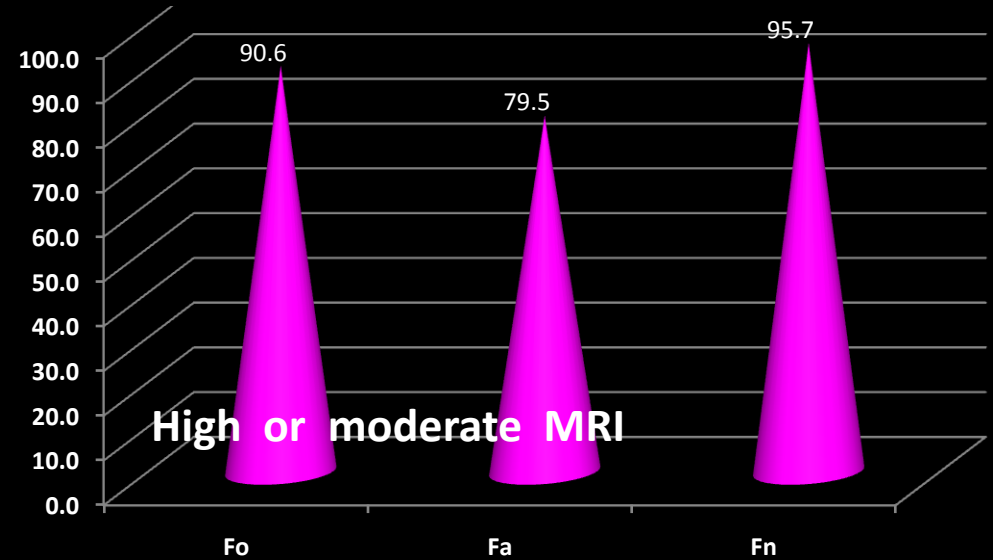
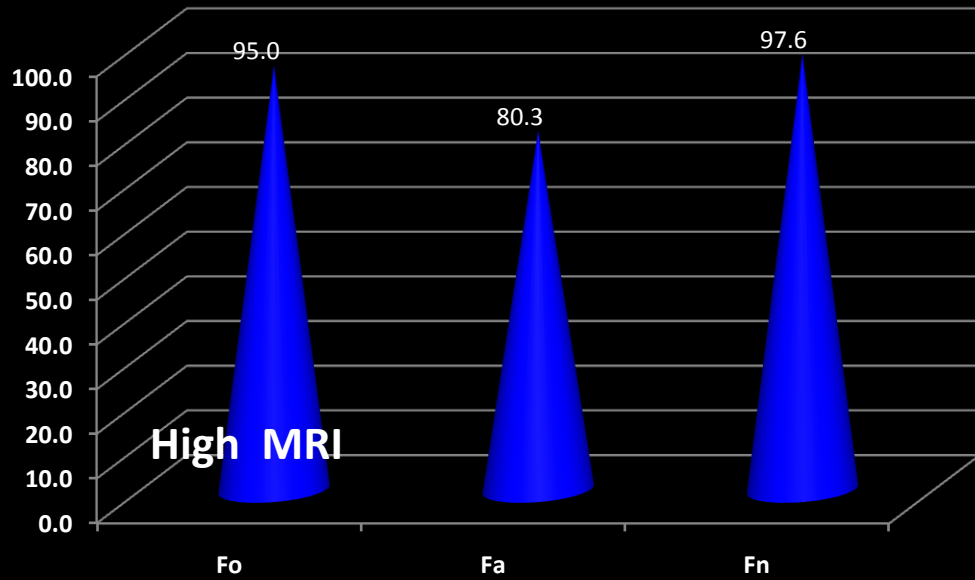
Sensitivity Fa of consensus ensemble prediction



Specificity Fn of consensus ensemble prediction



Average predictive ability



A detailed description of the consensus approach

Challenges and Advances
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Leonid Gorb
Victor Kuz'min
Eugene Muratov *Editors*

Application of Computational Techniques in Pharmacy and Medicine

 Springer

Chapter 12 Consensus Drug Design Using IT Microcosm

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Aida F. Kucheryavenko, Nataliya A. Gurova and Vera A. Anisimova

Abstract This chapter discusses Microcosm, an information technology package for predicting the pharmacological activity of chemical compounds. This technology is based on a complex prediction methodology with a consensus approach to prediction as its central component. The complex methodology of prediction in IT Microcosm is essentially different from that of other QSAR approaches in that it employs a redundant multi-descriptor, multi-level representation of the structure of chemical compounds by an aggregate of fragment descriptors with different physicochemical meanings and varying extents of complexity. The methodology also includes several classification methods that differ in their mathematical formalisms and several decision making circuits that are conceptual in the results they yield. At the same time, no feature space reductions are made, and no significant variables are isolated; all of the parameters of description are used in the construction of the prediction regularities. The integral decision rules are constructed by generalizing the spectrum of primary prediction estimates using different levels and types of consensus. In this chapter, we describe the paradigm of IT Microcosm, including its theoretical concepts, a specialized QL language for chemical structure representation, and prediction methods and strategies using the package. The adequacy, validity and high accuracy of IT Microcosm are demonstrated via sample predictions of the various pharmacological activities of structurally similar and structurally diverse organic compounds, complex organic salts, supramolecular complexes and substance mixtures, accounting for the synergy between the individual components of mixtures. The authors also present the results of a successful application of IT Microcosm, along with *in vivo* and *in vitro* experimental methods for (1) the search for novel potent antioxidants, antiarrhythmics and antiplatelet agents; (2) the optimization of the composition of supramolecular complexes with antioxidant and

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Free program Microcosm White

ИТ "Микрокосм" - прогноз свойств органических соединений

О программе

Входные данные **Прогноз**

Активности:

Выбранные:

Текущее состояние:
Выбор набора и параметров прогноза

Блок стратегий и методов прогноза

Прогноз по стратегии или по методу:

Стратегии Методы

Стратегия прогноз Метод прогноза:

консервативная Байеса

нормальная расстояния

рисковая ближайшего соседа

локального распределени

Способ тестирования:

автопрогноз

скользящий контроль

перекрестный контроль

двойной скользящий контроль


независимое тестировани

Вывод:

полный

таблица

строка



Microcosm White
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Т.М. Васильев,
А.И. Кочетков

**Свободно
распространяемая
версия**

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Thank you for attention!