System for Prediction of Pharmacokinetic Properties and Toxicity of Drug Compounds

Radchenko E.V., Karpov P.V., Sosnin S.B., Dyabina A.S., Sosnina E.A., Palyulin V.A., Zefirov N.S.

Department of Chemistry, Lomonosov Moscow State University

Institute of Physiologically Active Compounds RAS

Pharmacokinetic properties and toxicity (ADMET)

Absorption **Metabolism**
Distribution **Excretion** **Toxicity**

- Critically affect the efficacy, pharmacological profile, administration protocol and safety of drugs
- Optimization of these properties is an important aspect of drug discovery and development
- Ability to predict them for new structures can substantially improve the speed and efficiency of drug development

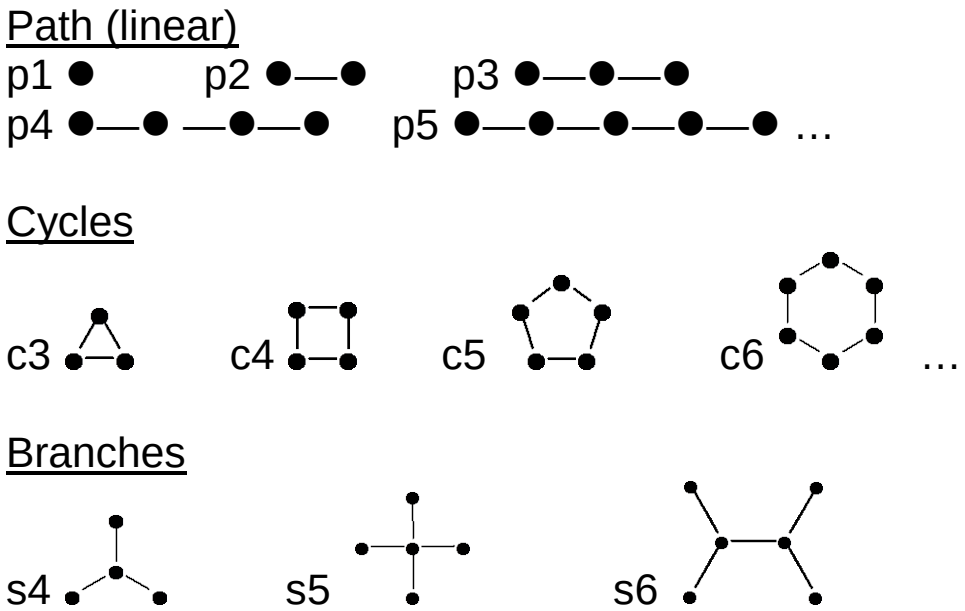
Prediction of ADMET properties

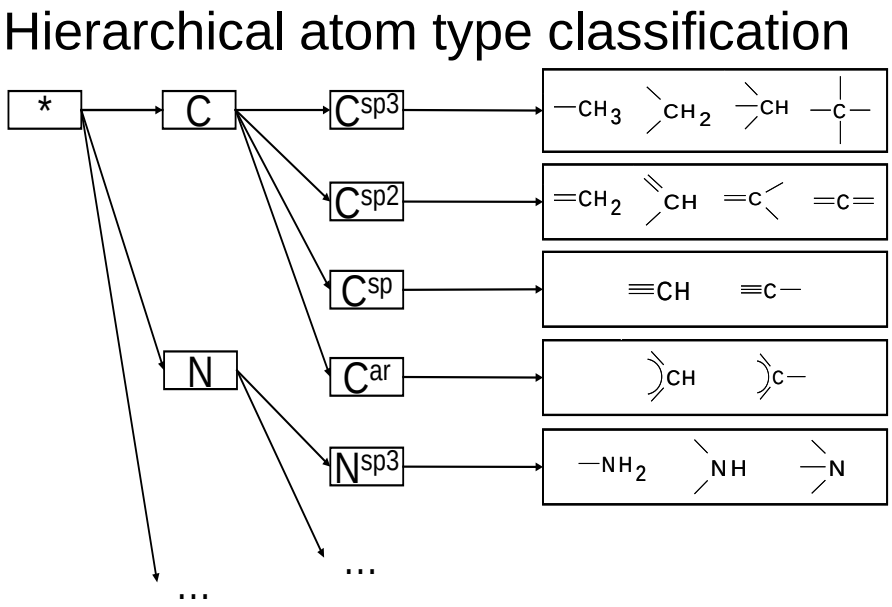
General prediction methodology based on the QSAR/QSPR approaches

- Extensive and verified experimental data sets
- Nonlinear modeling of the structure-property relationships using artificial neural networks
- Flexible structure description based on the fragmental descriptors

- **High prediction accuracy and efficiency**
- **Broad applicability domain**
- **Even for diverse compounds with varying (and/or incompletely characterized) mechanisms of action**

Fragmental (substructural) descriptors

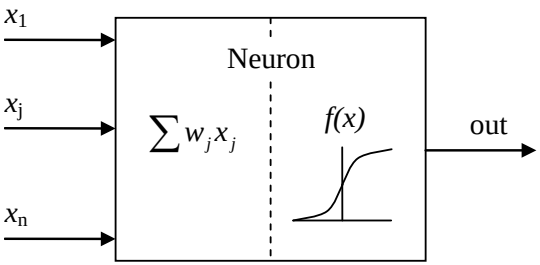


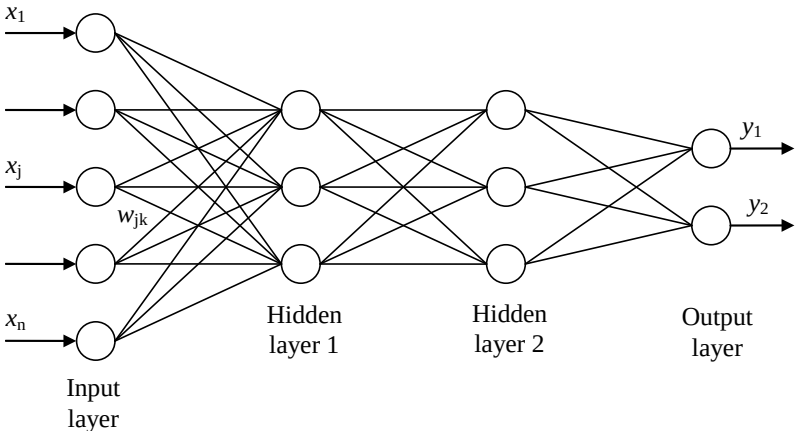


- Thousands of fragments
- “Holographic portrait” of a molecule
- Applicable to diverse series of compounds
- Easy prediction for new compounds
- Simple structural interpretation

Artificial neural networks

- Generic modeling of nonlinear structure–property/activity (QSAR/QSPR) relationships





- Descriptor preselection by multiple linear regression
- Predictivity assessment using double cross-validation
- Selection of optimal network architecture and descriptor set
- Reliable prediction using ensemble of trained networks
- Estimation of individual descriptor contributions for interpretation purposes

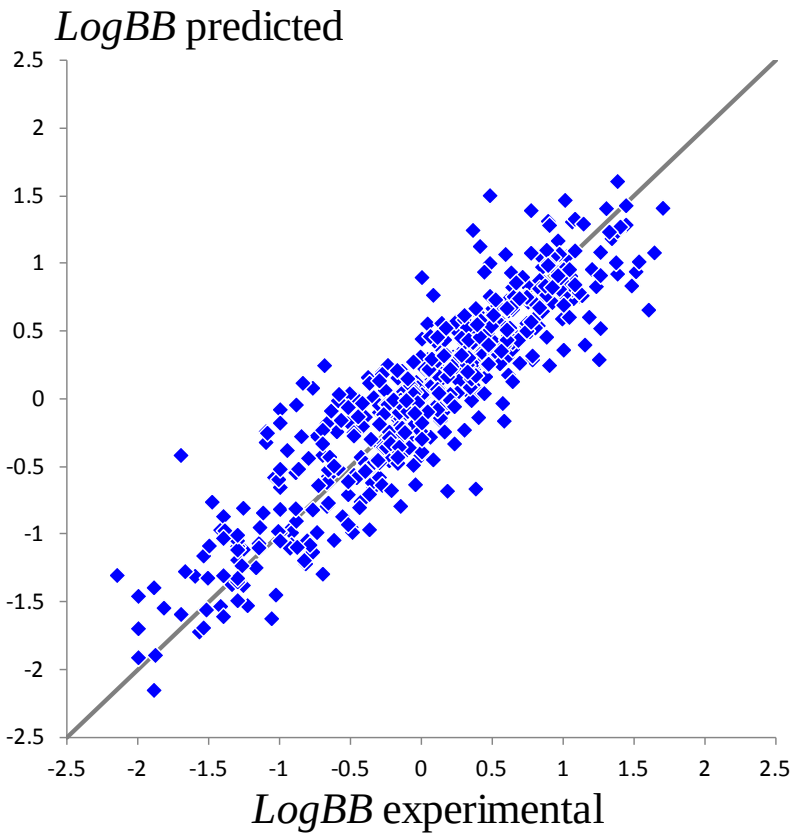
Blood-brain barrier (BBB) permeability

Probably the most complete data set based on open quantitative published data – verified against original publications

Different transport mechanisms are not considered explicitly

Comparable or better in accuracy and/or applicability domain compared to previously published models

$$LogBB = \frac{C_{brain}}{C_{blood}}$$



N = 529, Q^2 = 0.82, $RMSE$ = 0.32

Abraham, 2006

N = 292, R^2 = 0.75, $RMSE$ = 0.33

Garg, 2008

N = 132, Q^2 = 0.79, $RMSE$ = 0.33

Muehlbacher, 2011

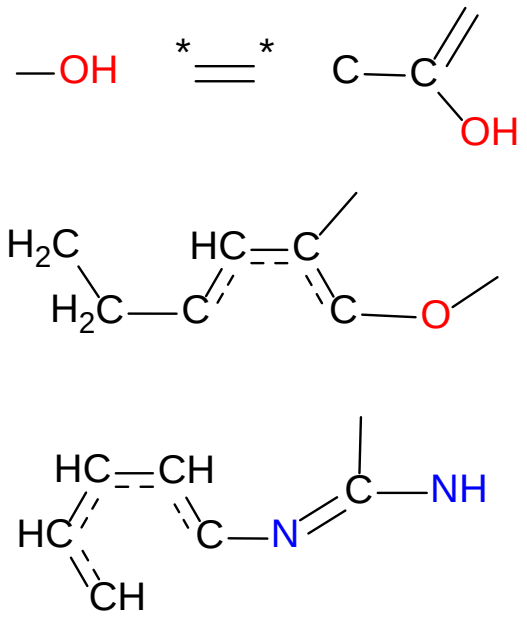
N = 352, Q^2 = 0.55

Dyabina A.S., Radchenko E.V., Palyulin V.A., Zefirov N.S., *Dokl. Biochem. Biophys.*, 2016, 470, in press.

Blood-brain barrier (BBB) permeability

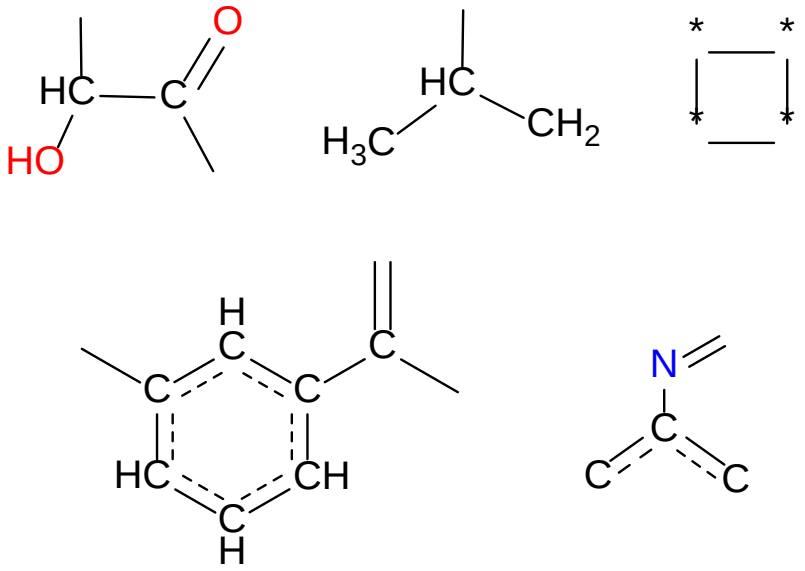
Reasonable interpretation of major fragment contributions

Decrease LogBB



Polar groups

Increase LogBB



Hydrophobic groups, active transport of substituted monocarboxylic acids

Blood-brain barrier (BBB) permeability

Good validation results on independent test set (*)

Estimated qualitative data: BBB+ / BBB–

LogBB predictions converted to qualitative scale using the cut-off value LogBB = –1

Correctly recognized more than 90% of BBB+ componds

Lower prediction quality for BBB– (partly due to often approximate indirect estimates in the test set)

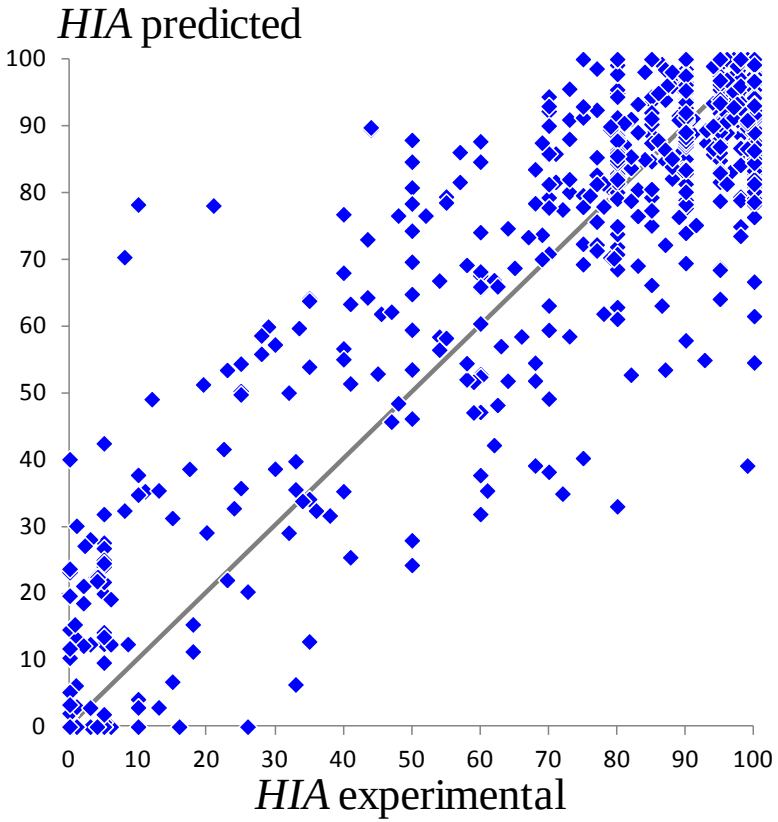
	Prediction: full set		**Prediction: no overlap**	
	BBB+	**BBB–**	**BBB+**	**BBB–**
Actual BBB+	*TP* = 1464	*FN* = 105	*TP* = 1255	*FN* = 100
Actual BBB–	*FP* = 281	*TN* = 203	*FP* = 259	*TN* = 192
Total	2053		1806	
Overall accuracy	81%		80%	
Sensitivity	93%		93%	
Specificity	42%		43%	

(*) Martins I.F., Teixeira A.L., Pinheiro L., Falcao A.O., *J. Chem. Inf. Mod.*, 2012, 52 (6), 1686-1697.

Human intestinal absorption (HIA)

Probably the most complete data set based on open data
Less uniform distribution of data
(for 60% of compounds HIA > 80%)
Different transport mechanisms are not considered explicitly
Comparable or better in accuracy and/or applicability domain compared to previously published models

$$HIA = \frac{D_{blood}}{D_{dose}}$$



N = 708, Q^2 = 0.80, $RMSE$ = 13.8

Hou, 2007

N = 435, R^2 = 0.76, $RMSE$ = 12.7

Yan, 2008

N = 552, R^2 = 0.79, $RMSE$ = 16.4

Moda, 2011

N = 638, Q^2 = 0.67, $RMSE$ = 11.2

Radchenko E.V., Dyabina A.S., Palyulin V.A., Zefirov N.S., *Russ. Chem. Bull.*, 2016, in press

hERG-mediated cardiotoxicity risk

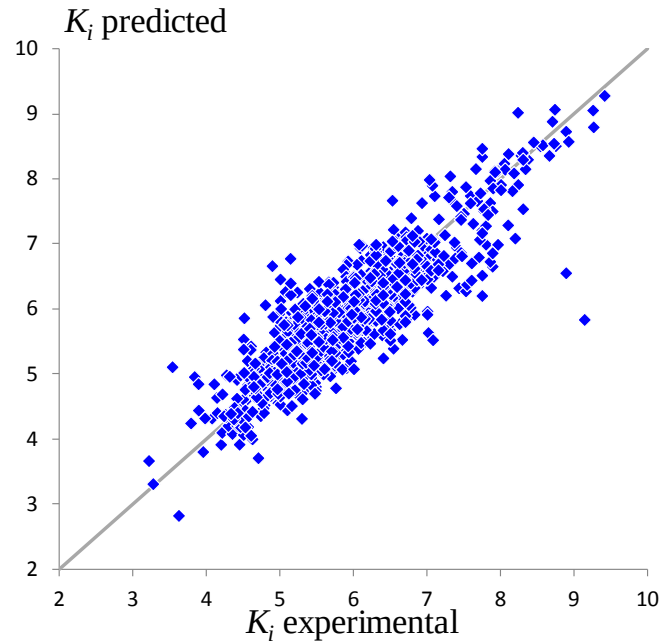
hERG potassium channel is among the most important antitargets in drug development

Probably the most complete data set based on open data

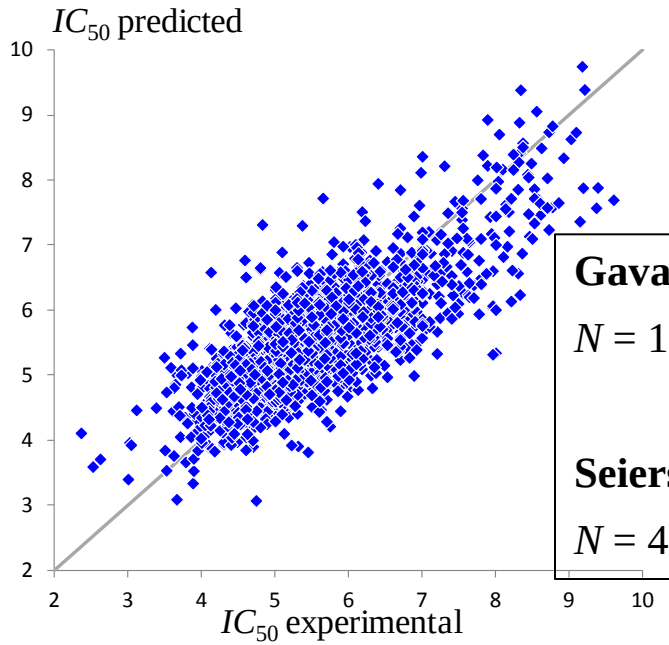
Affinity (K_i) or functional (IC_{50}) assays

Comparable or better in accuracy and/or applicability domain compared to previously published models

***pK_i*: N = 1000, Q^2 = 0.77, *RMSE* = 0.45**



***pIC_{50}*: N = 2886, Q^2 = 0.60, *RMSE* = 0.55**



Gavaghan, 2007 (*pIC_{50}*)

N = 1312, Q^2 = 0.48, *RMSE* = 0.49

Seierstad, Agrafiotis, 2006 (*pIC_{50}*)

N = 439, Q^2 = 0.67, *RMSE* = 0.02

Radchenko E.V., Rulev Yu.A., Safanyaev A.Ya., Palyulin V.A., Zefirov N.S., *Dokl. Biochem. Biophys.*, 2016, in press.

Integrated Web platform for ADMET properties prediction

- Structure entry
- Descriptor calculation
- Property prediction
- Result visualization and preliminary analysis

- http://qsar.chem.msu.ru/admet/

Integrated Web platform for ADMET properties prediction

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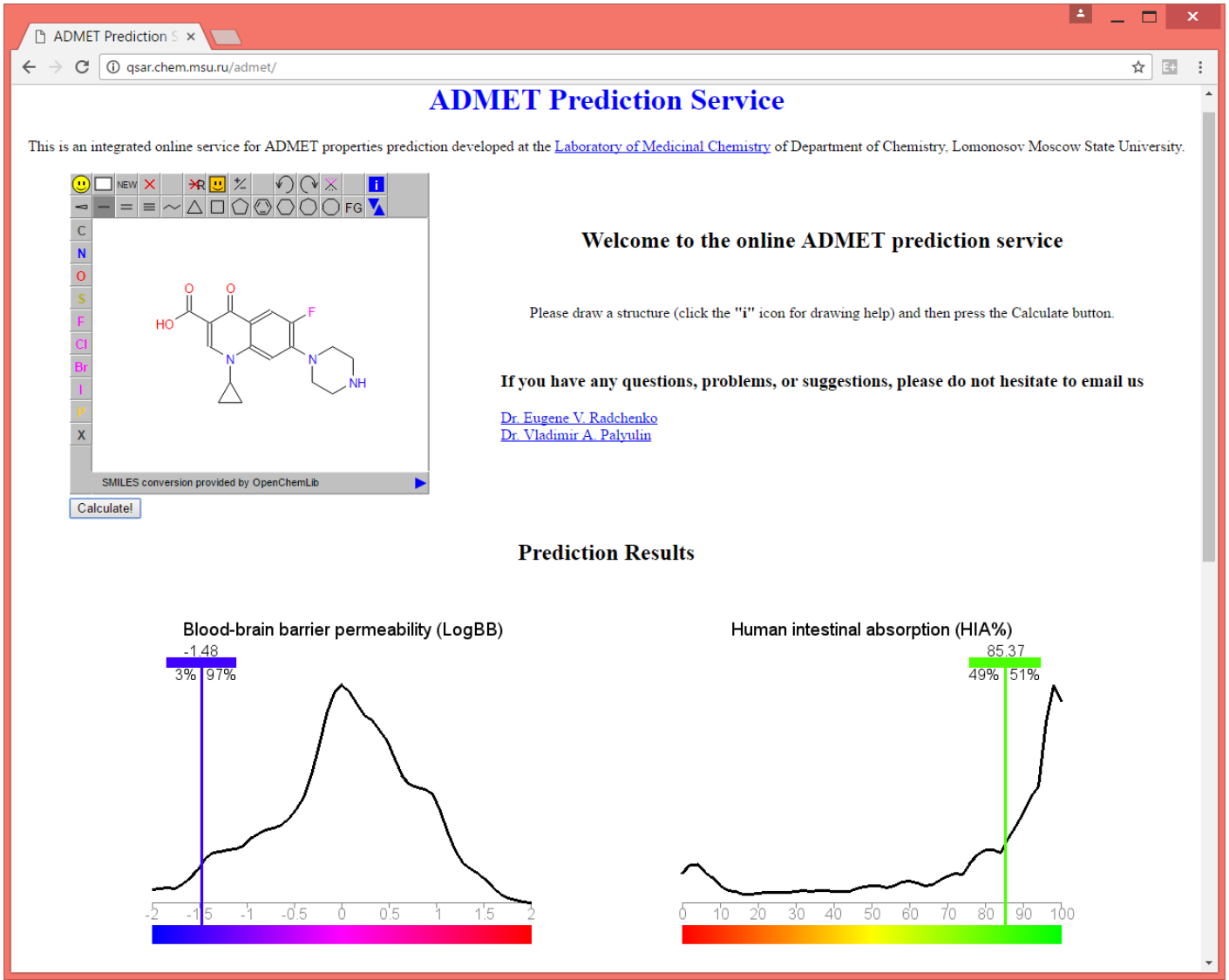
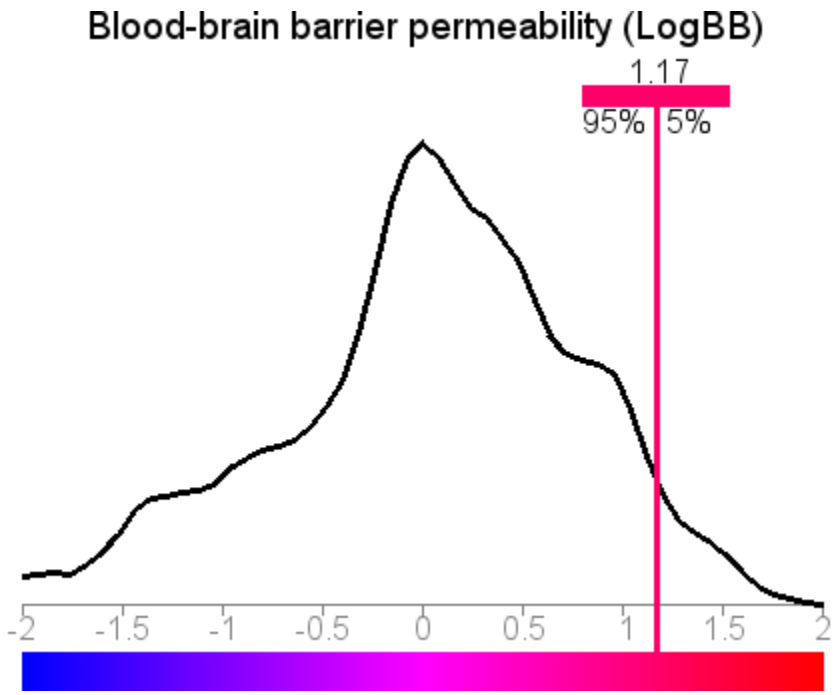
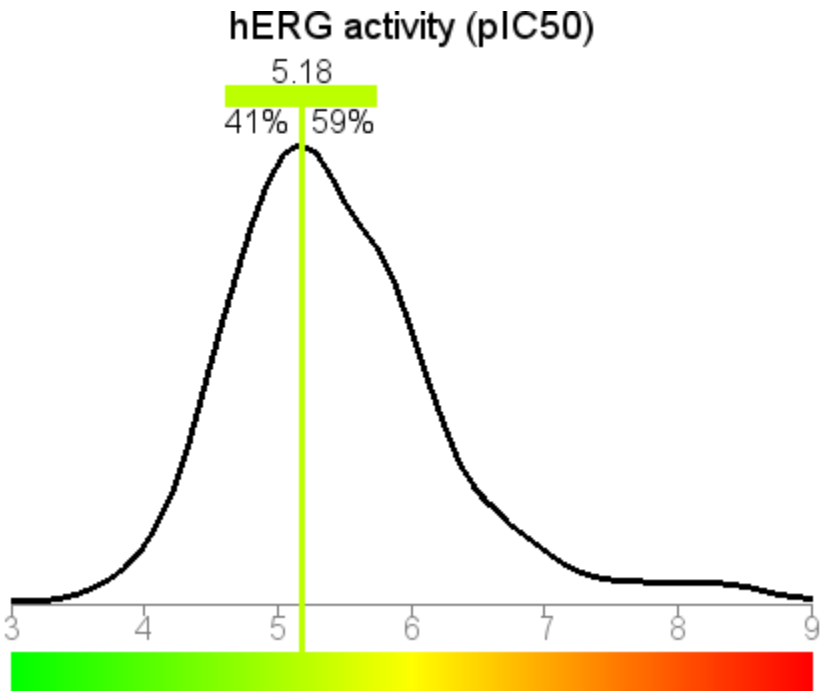


Integrated Web platform for ADMET properties prediction

- Parameter name
- Predicted value
- Color scale (good/bad or low/high) and compound position
- Parameter distribution for known (training set) compounds
- Fraction of compounds below/above predicted value





Integrated Web platform for ADMET properties prediction

- Blood-brain barrier (BBB) permeability
- Human intestinal absorption (HIA)
- hERG-mediated cardiotoxicity risk

- Lipophilicity (LogP)
- Plasma protein binding (HSA)
- Aromatic hydrocarbon receptor (AhR) binding
- Mutagenicity
- Acute toxicity
- Cytotoxicity
- ……
- **Enhanced result analysis**

Conclusions

- General QSAR/QSPR methodology is suitable for the construction of **predictive models** relating the structures of drug compounds to their **pharmacokinetic properties and toxicity** (ADMET parameters)
- An integrated **Web-based prediction system** developed by us supports convenient prediction of a number of **important ADMET parameters**
- The service is **freely accessible** and may be used for the research in various areas of **medicinal chemistry and pharmacology**

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Thank you
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