Determining Biologically Relevant Effects of Compound Exposure by Chemical, Biological and Phenotypic Data Integration

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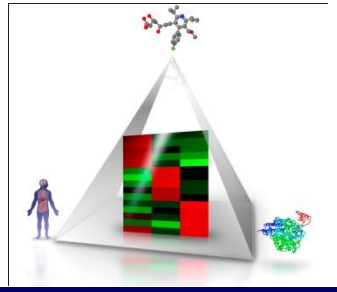


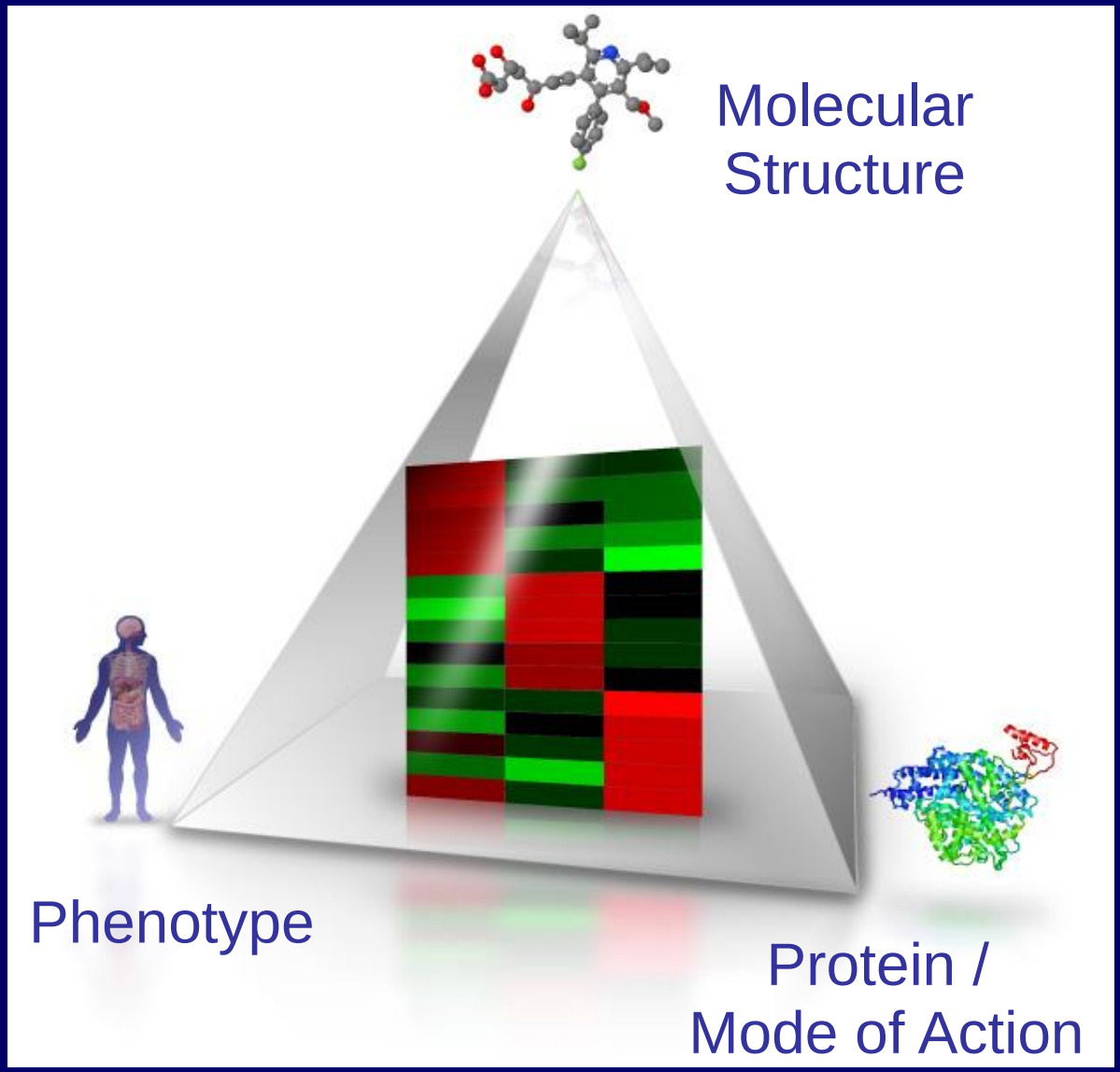
More and More Data is Available...

- But how should we deal with it?
- Companies (but now also the public databases) have tens of millions of bioactivity data points, gene expression data, organ tox endpoint data, clinical trial data, ...

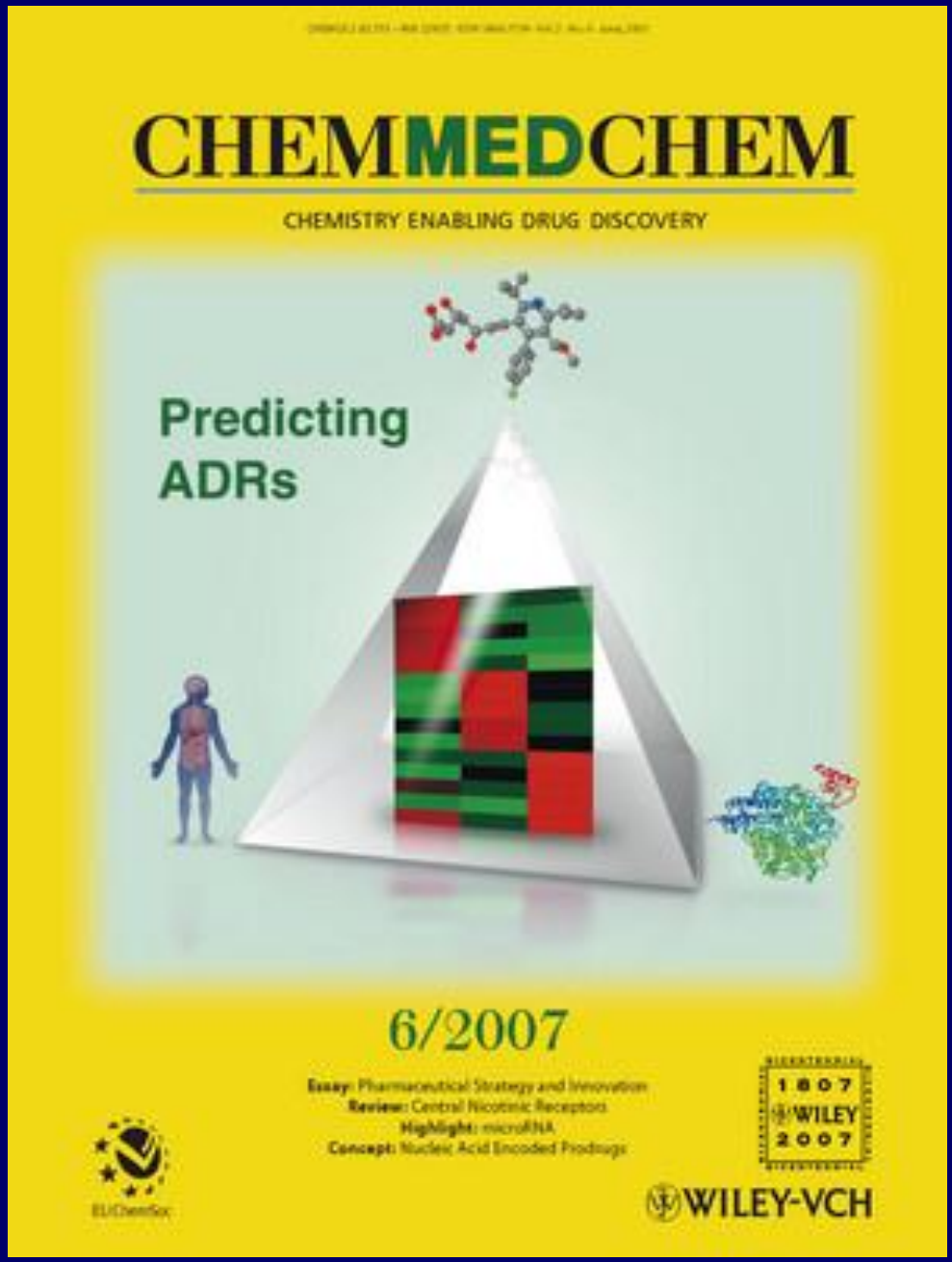
- *However*, integration – and utilization – of data is often not ideal

- In our group we are exploring ways to integrate data from different sources to understand bioactivities, and to design novel chemistry

The ‘Magic Triangle’ – Our Primary Data Sources



So what do we do? Predict compound properties, such as adverse reactions…

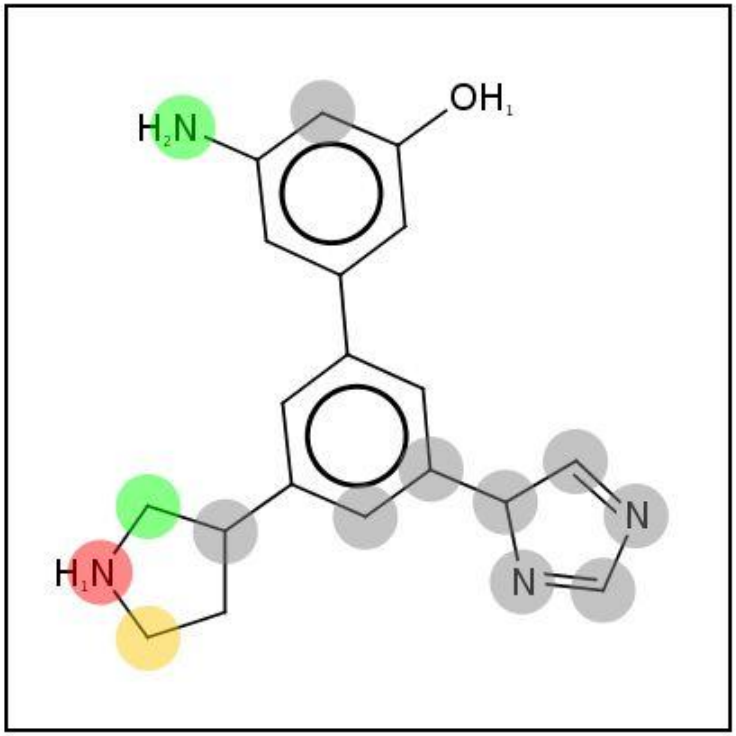


… or predicting metabolites (and their bioactivities); www-metaprint2d.ch.cam.ac.uk

MetaPrint2D
metabolic site predictor

University of Cambridge › Department of Chemistry › Unilever Centre for Molecular Science Informatics

Results



Move the cursor over an atom for detailed results.

Input

SMILES: Nc4cc(O)cc(c3cc(C1C=NC=N1)cc(C2CCNC2)c3)c4
Model: METAB20081ALL
Settings: DEFAULT

Instructions

The colour highlighting an atom indicates its normalised occurrence ratio (NOR). A high NOR indicates a more frequently reported site of metabolism in the metabolite database.

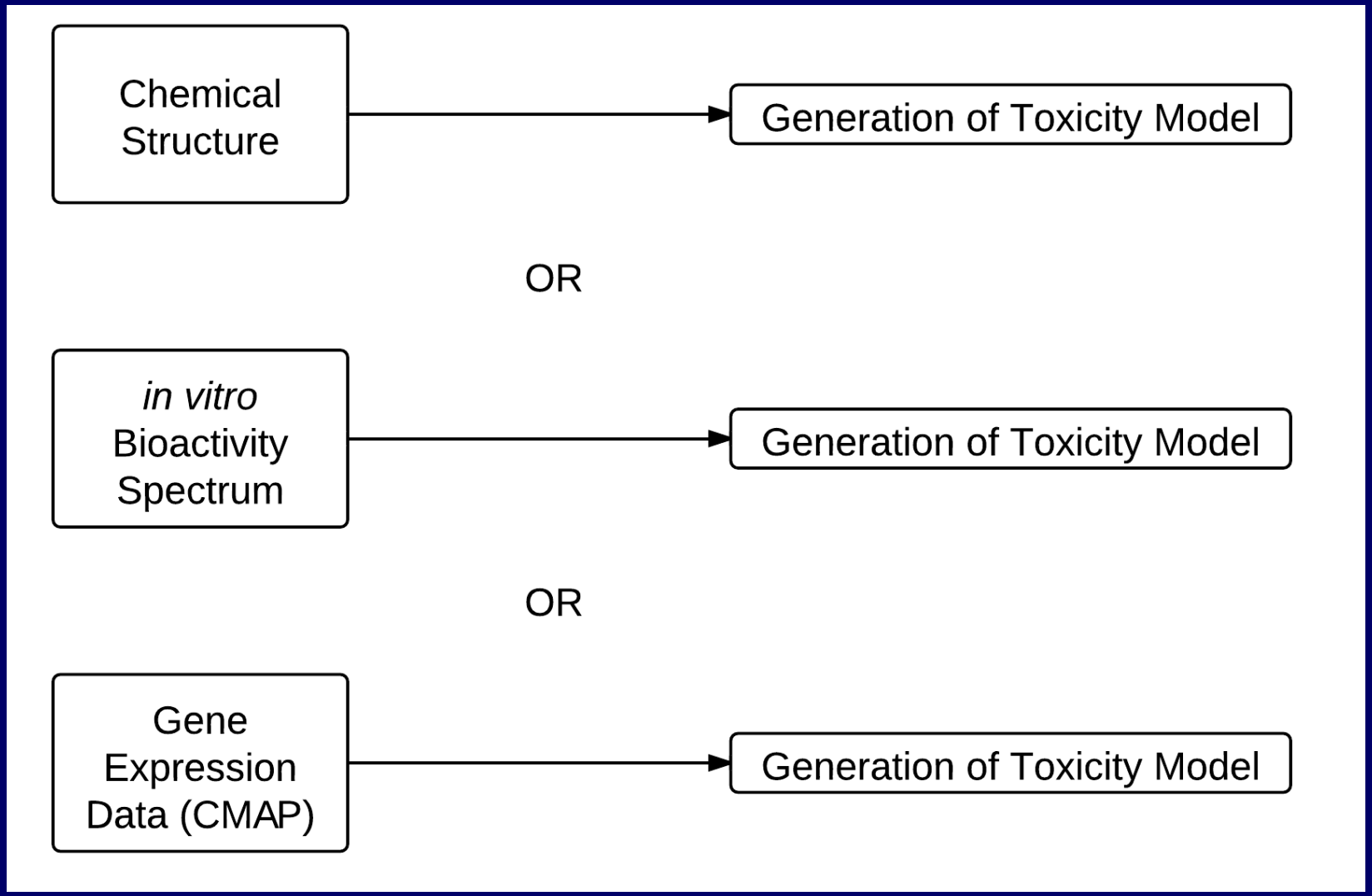
Note: The normalised occurrence ratio does not indicate how likely a molecule is to be metabolised, but rather the relative likelihood of metabolism occurring at a particular site in the molecule, assuming it is metabolised.

Results Colour Scheme

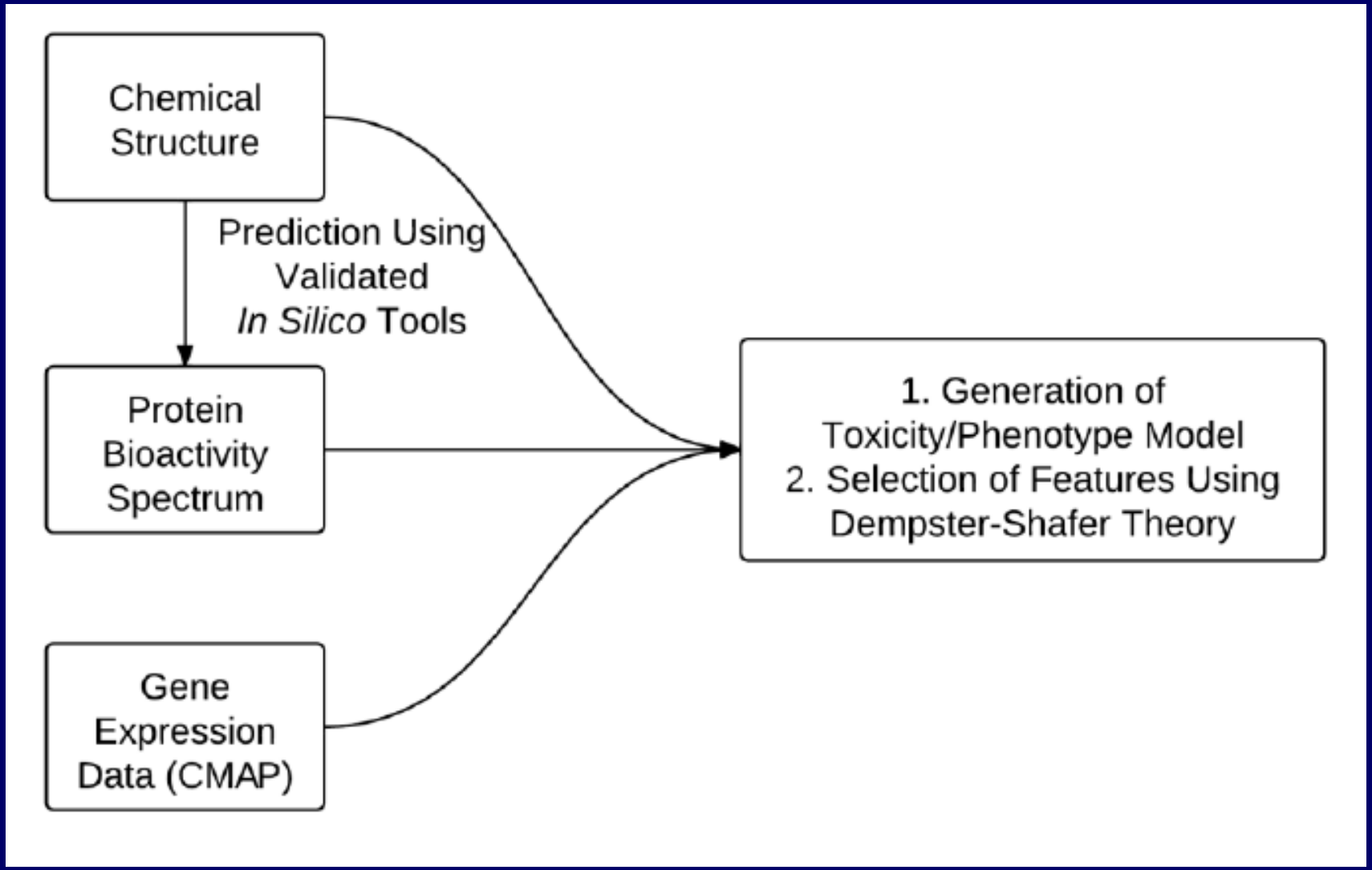
Red	0.66 <= NOR <= 1.00
Orange	0.33 <= NOR < 0.66
Green	0.15 <= NOR < 0.33
White	0.00 <= NOR < 0.15
Grey	Little/no data

Links
- New Query
- Predict metabolites *(experimental)*
- About MetaPrint2D
- sourceforge project
- bioclipse plugin

What has been done *previously*? Toxicity models are based on *single-domain* data

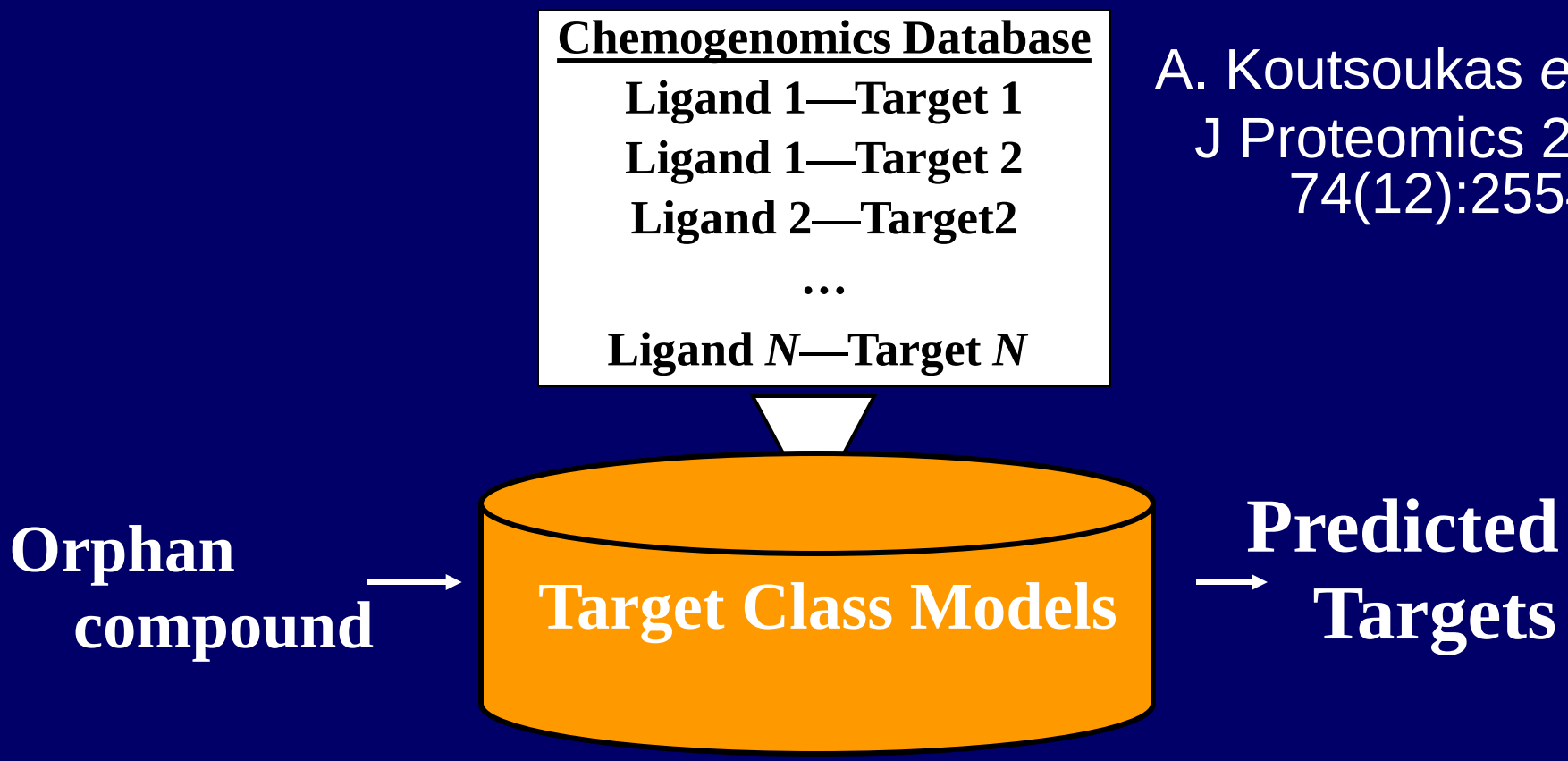


Not ‘OR’ – Different Information Contents, Hence *AND*!



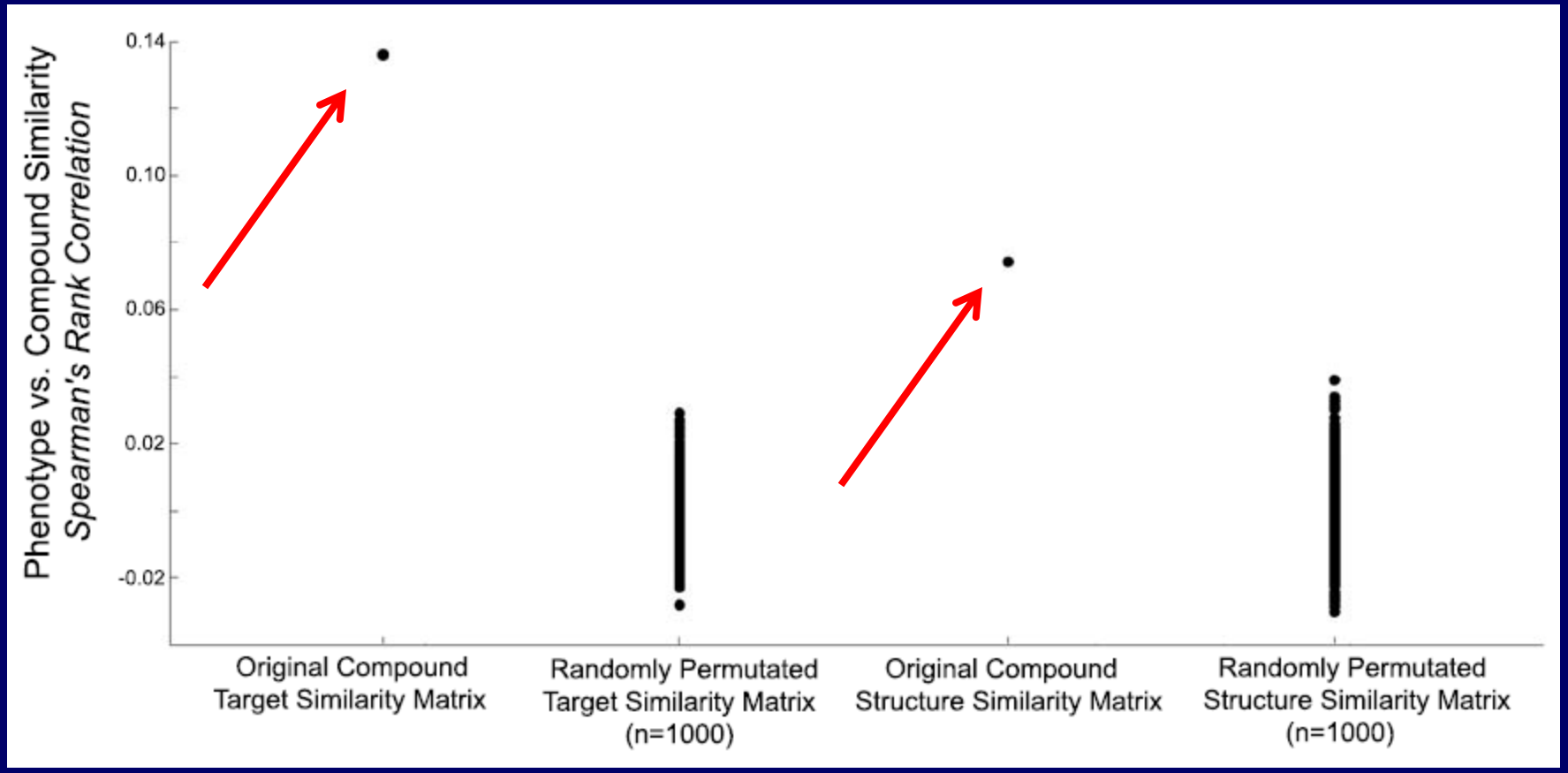
Exploiting known bioactivity data for new decisions: Target predictions

• The models enable automated prediction of the targets or target families of orphan ligands given only their chemical structures.



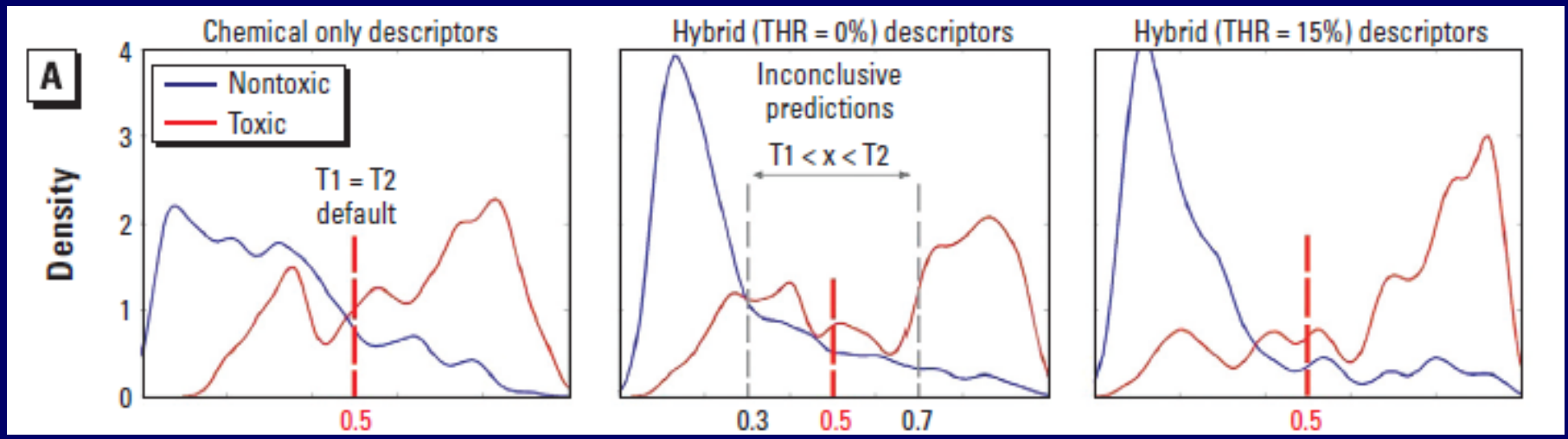
A. Koutsoukas *et* al., J Proteomics 2011, 74(12):2554-74

Higher Correlation of Predicted Targets Than Structures With Phenotypes



Young, Bender et al., Nature Chem. Biol. 2008, 4, 59 - 68

Sedykh *et al.* 2011: Chemical + *in vitro* descriptors for rat LD50 prediction



Use of in Vitro HTS-Derived Concentration–Response Data as Biological Descriptors Improves the Accuracy of QSAR Models of in Vivo Toxicity, A. Sedykh *et al.*, Environ. Health Persp., 2011, 119 (3), 364 – 370

How? Use of Funding, Data Sources

- PhD Student financed by the award; started his work last month (October 2012)

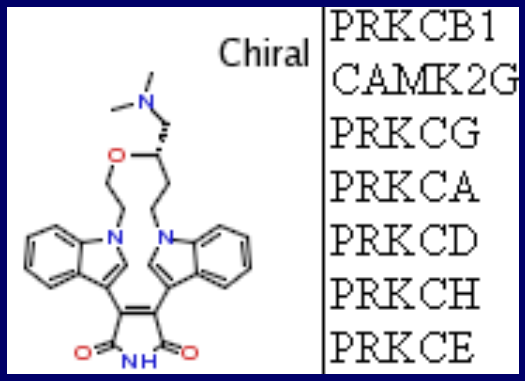
- Previous literature datasets

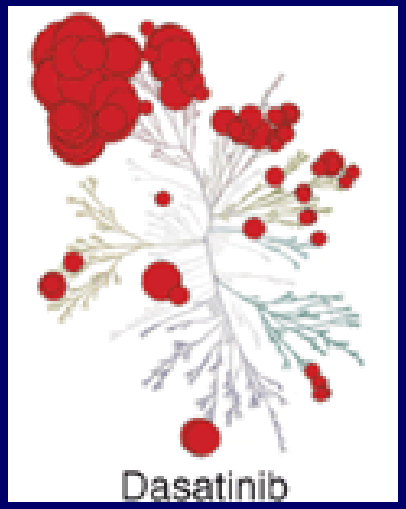
- ToxCastDB + ToxRefDB (Assays, Animal Data)
  - ToxRefDB (30 years and $2 billion worth of animal toxicity studies)
  - ToxCastDB (data from screening 1,000 chemicals in over 500 high-throughput assays)

- Unspecific effects; dose/time (PK/PD) are (current) limitations of the project

Relating chemistry, targets and phenotypes

- We have information from chemistry, biology, and phenotypes
- *Joint modeling* very likely improves predictivity (see preliminary results)
- This is the goal of this project





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