Safer Chemicals Design Diagrams

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Safer Chemicals Design Targeting NRF2-ARE Pathway

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MoDRN Molecular Design Research Network

Introduction

- High throughput screening (HTS) assays can be used to probe the effect of chemicals acting on cells and infer *in vivo* toxicity.
- The U.S. EPA ToxCast program is building a large collection of *in vitro* HTS assay data for very diverse chemicals. [1-3]
- The NRF2-ARE antioxidant pathway is an important biological sensing and regulating system in response to xenochemicals.
- When the external disruption exceeds the inherent resilience of the biological system, cellular damage can occur, eventually leading to cytotoxicity.[4]
- The No. 4 Principle of Green Chemistry aims at designing molecules with reduced toxic potentials.[5]
- This presentation is about a coupled diagram to guide safer chemicals design with less chance to incur cytotoxicity and perturb NRF2-ARE pathway.

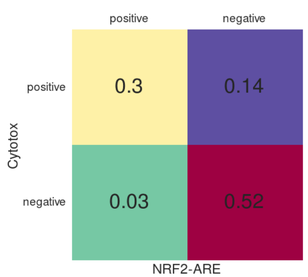
Data Preparation

Data Source :

- U.S. EPA ToxCast and Tox21 database
- M.W. range 50∼1000
- Total number of chemical entries > 1200

Correlation Diagrams

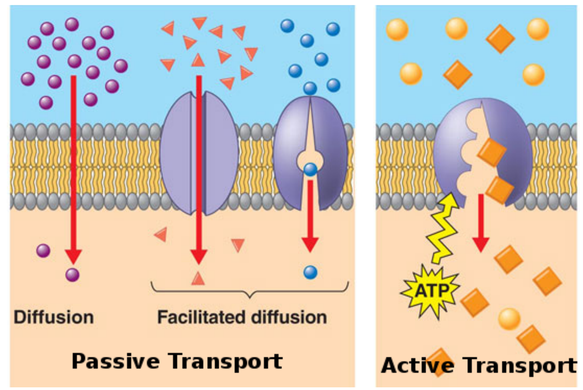
between two assays



between two endpoints

Theory

pH partition hypothesis[6]



source : http://alenaimp.blogspot.com/2012/03/diffusion-active-transport-and-osmosis.html

Thermodynamic Force

$$F = -\frac{RT}{c}\left(\frac{\partial c}{\partial x}\right)_{p,T}$$

Fick's Law

$$J = -D\frac{dc}{dx} = s\,c$$

Density Functional Theory

$$dE = \left(\frac{\partial E}{\partial N}\right) dN + \int \left(\frac{\partial E}{\partial v(\boldsymbol{r})}\right)_N \delta v(\boldsymbol{r}) d(\boldsymbol{r})$$

Statistical Modeling

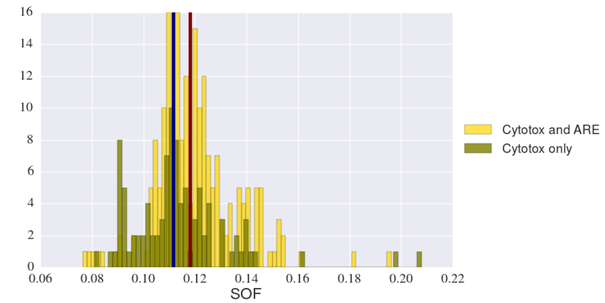
$$\pi(X) = \frac{\exp(\sum_{i=0}^{n} \beta_i X_i^i)}{1 + \exp(\sum_{i=0}^{n} \beta_i X_i^i)}$$

References

[1] D. J. Dix, K. A. Houck, M. T. Martin, A. M. Richard, R. W. Setzer, R. J. Kavlock. Toxicol. Sci. (2007) 95, 5. [2] R. S. Judson, K. A. Houck, R. J. Kavlock, T. B. Knudsen, M. T. Martin, H. M. Mortensen, *et al.* Environ. Health Perspect. (2010) 118, 485 [3] R. Kavlock, K. Chandler, K. Houck, S. Hunter, R. Judson, N. Kleinstreuer (2012) 25, 1287 [4]] L. Q. Shen, R. Judson, F. Menlikov, J. Roethle, A. Gudibanda, J. B. Zimmerman and P. T. Anastas, Green. Chem., 2016. DOI:10.1039/C6GC01058J. [5] Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice. 1998. [6] L. S. Schanker, D. J. Tocco, B. B. Brodie, C. A. M. Hogben. J. Pharm. Exp. Ther. (1958) 123, 81

Model and Design

- Mechanistic Insight



molecular softness can distinguish the two groups of chemicals of interest

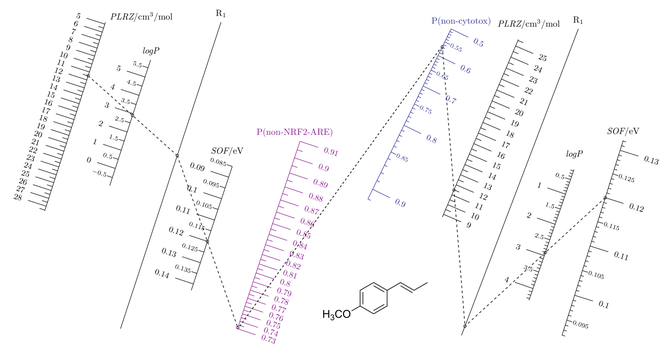
- Model Evaluation

$$\text{precision} = \text{true positive}/(\text{true positive} + \text{false positive})$$

$$\text{recall} = \text{true positive}/(\text{true positive} + \text{false negative})$$

measure	precision	accuracy	ROC AUC
cross validation	0.86±0.04	0.80±0.03	0.81±0.04
external evaluation	0.90	0.78	0.81

- Design Diagram



coupled diagram to guide chemical design with reduced toxicity

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