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Safer Chemicals Design Diagrams

Longzhu Shen

Yale University, longzhu.shen@yale.edu

Fjodor Melnikov

Yale University

John Roethle

Yale University

Aditya Gudibanda

Yale University

Richard Judson

US EPA

See next page for additional authors

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Presenter/Creator Information

Longzhu Shen, Fjodor Melnikov, John Roethle, Aditya Gudibanda, Richard Judson, Julie Zimmerman, and Paul Anastas

Safer Chemicals Design Targeting NRF2-ARE Pathway

L. Q. Shen,^a F. Melnikov,^a J. Roethle,^a A. Gudibanda,^a R. S. Judson,^b J. B. Zimmerman,^a and P. T. Anastas^{a*}

^aYale University, CT 06511 ^bU.S. EPA, National Center for Computational Toxicology, RTP NC 27711



INTRODUCTION

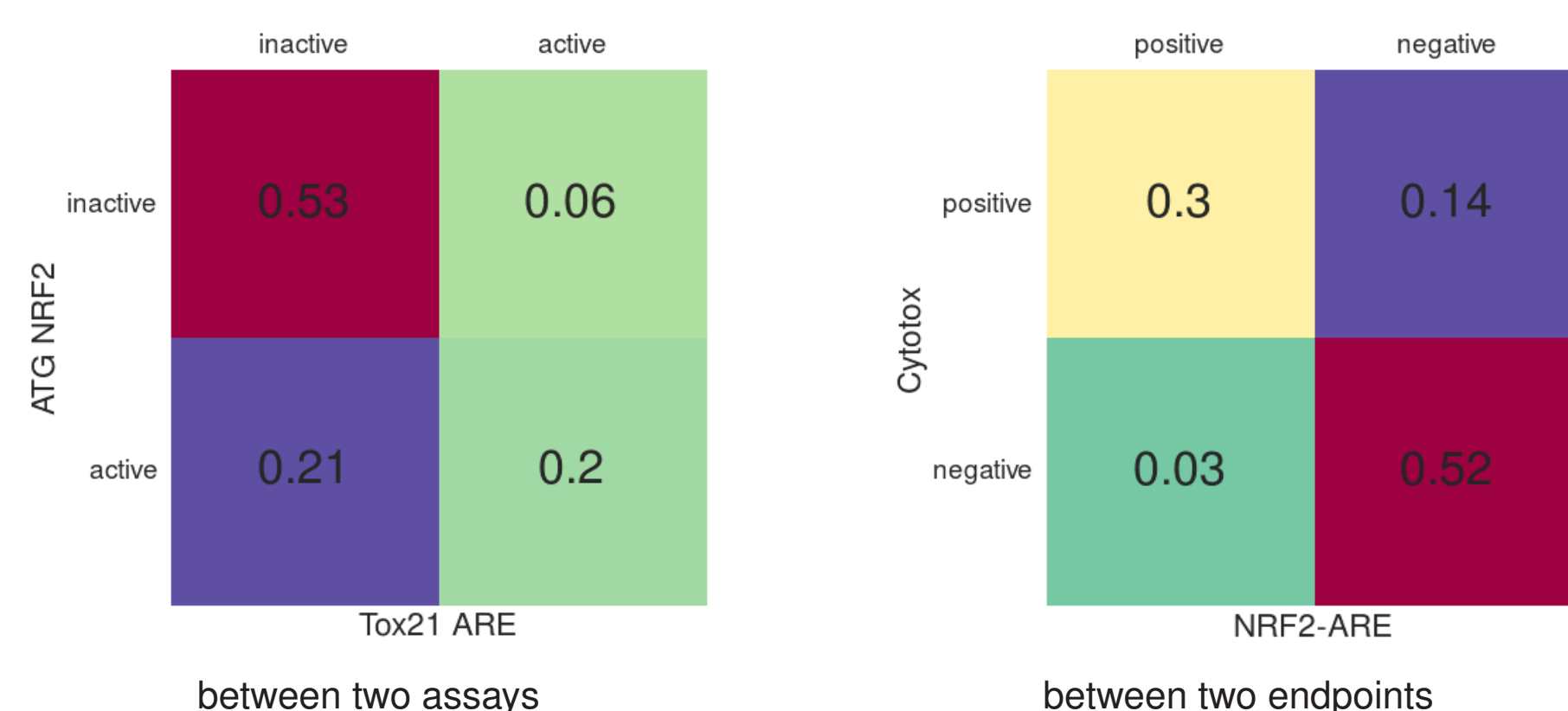
- High throughput screening (HTS) assays can be used to probe the effect of chemicals acting on cells and infer *in vivo* toxicity.
- The U.S. EPA ToxCast program is building a large collection of *in vitro* HTS assay data for very diverse chemicals.¹⁻³
- The NRF2-ARE antioxidant pathway is an important 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 :

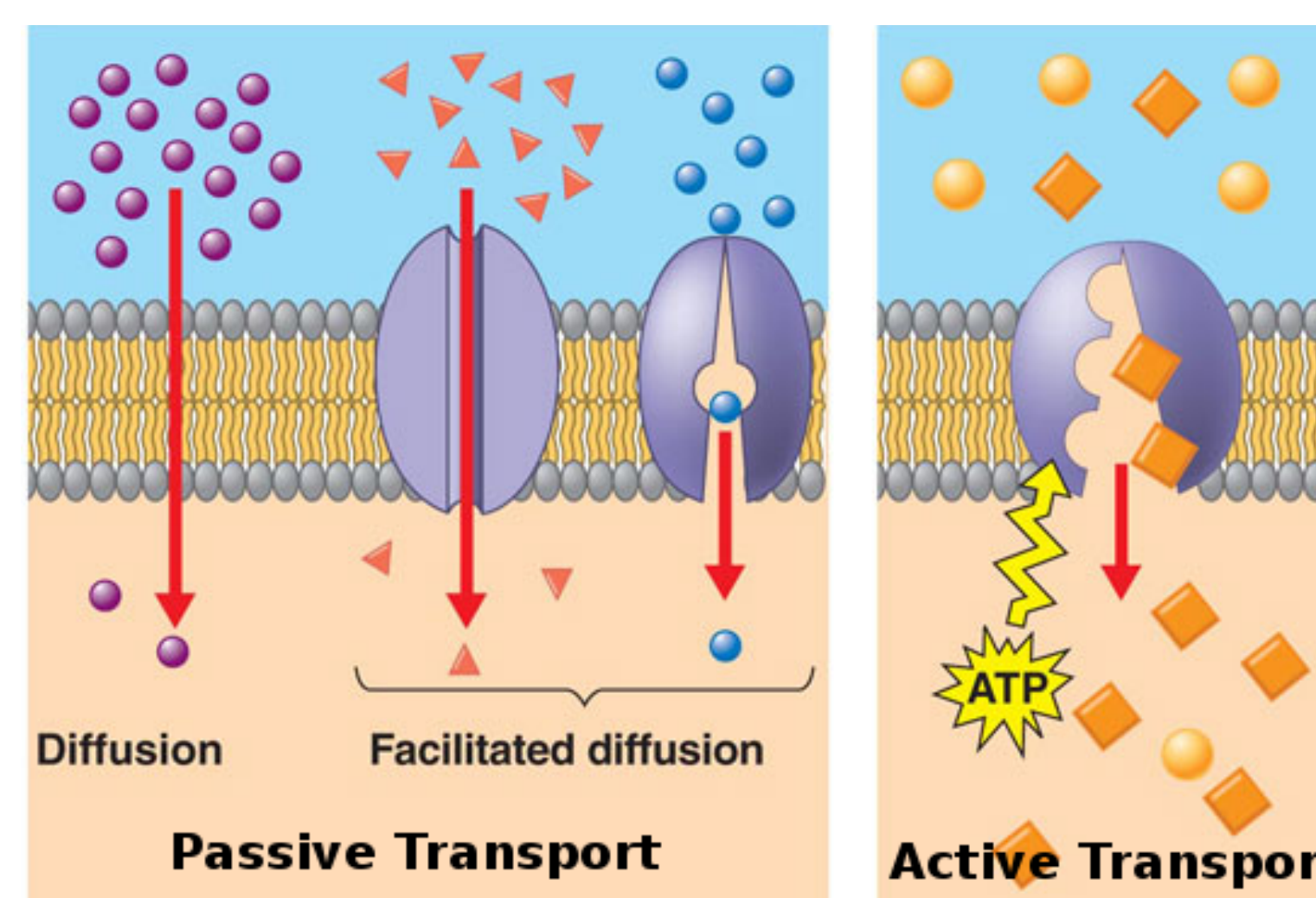
- U.S. EPA ToxCast and Tox21 database
- M.W. range 50~1000
- Total number of chemical entries > 1200

Correlation Diagrams



THEORY

pH partition hypothesis⁶



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

$$J = -D \frac{dc}{dx} = sc$$

Density Functional Theory

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

Statistical Modeling

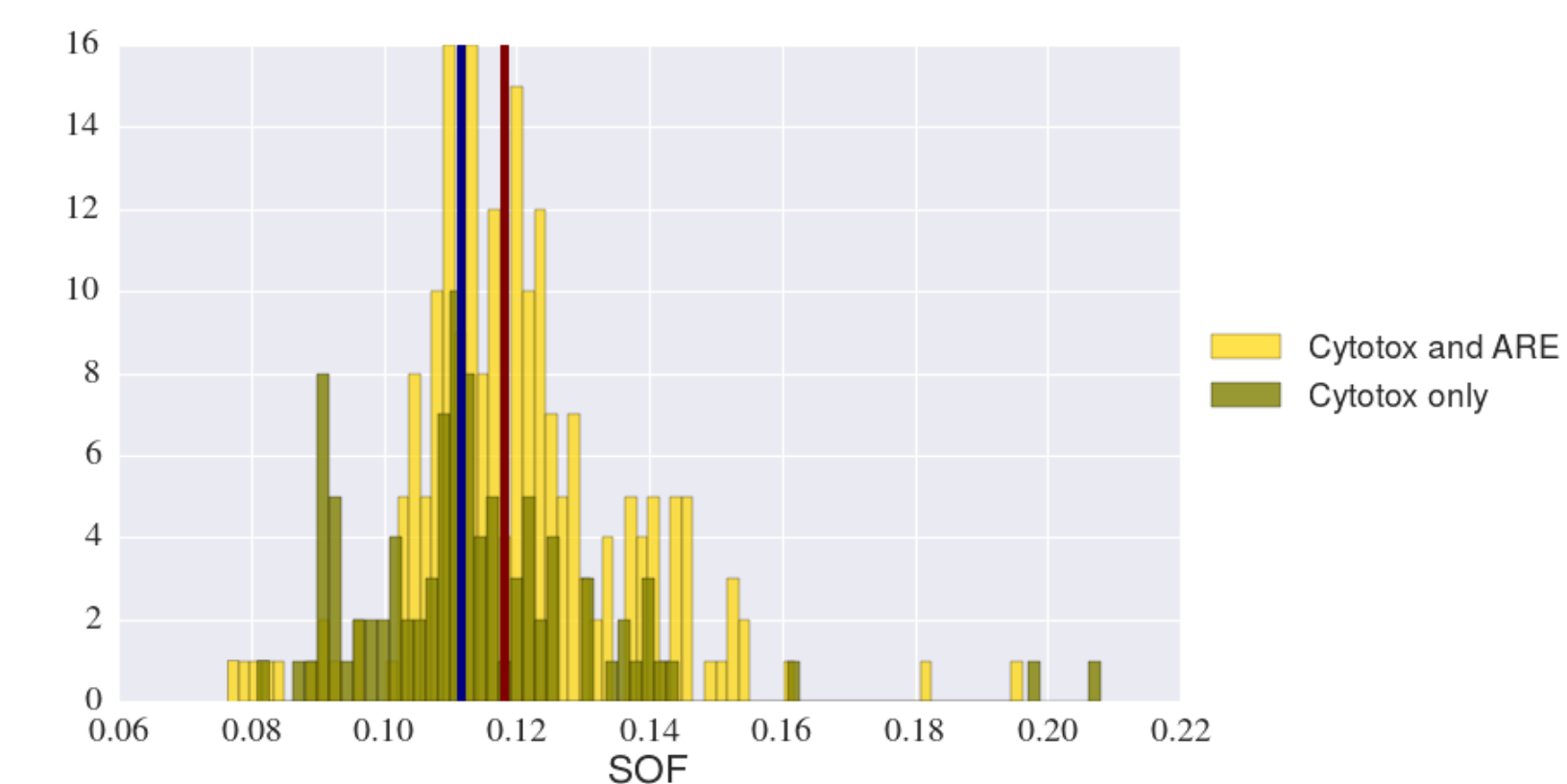
$$\pi(X) = \frac{\exp(\sum_{i=0}^n \beta_i X_i^i)}{1 + \exp(\sum_{i=0}^n \beta_i X_i^i)}$$

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. Melnikov, 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

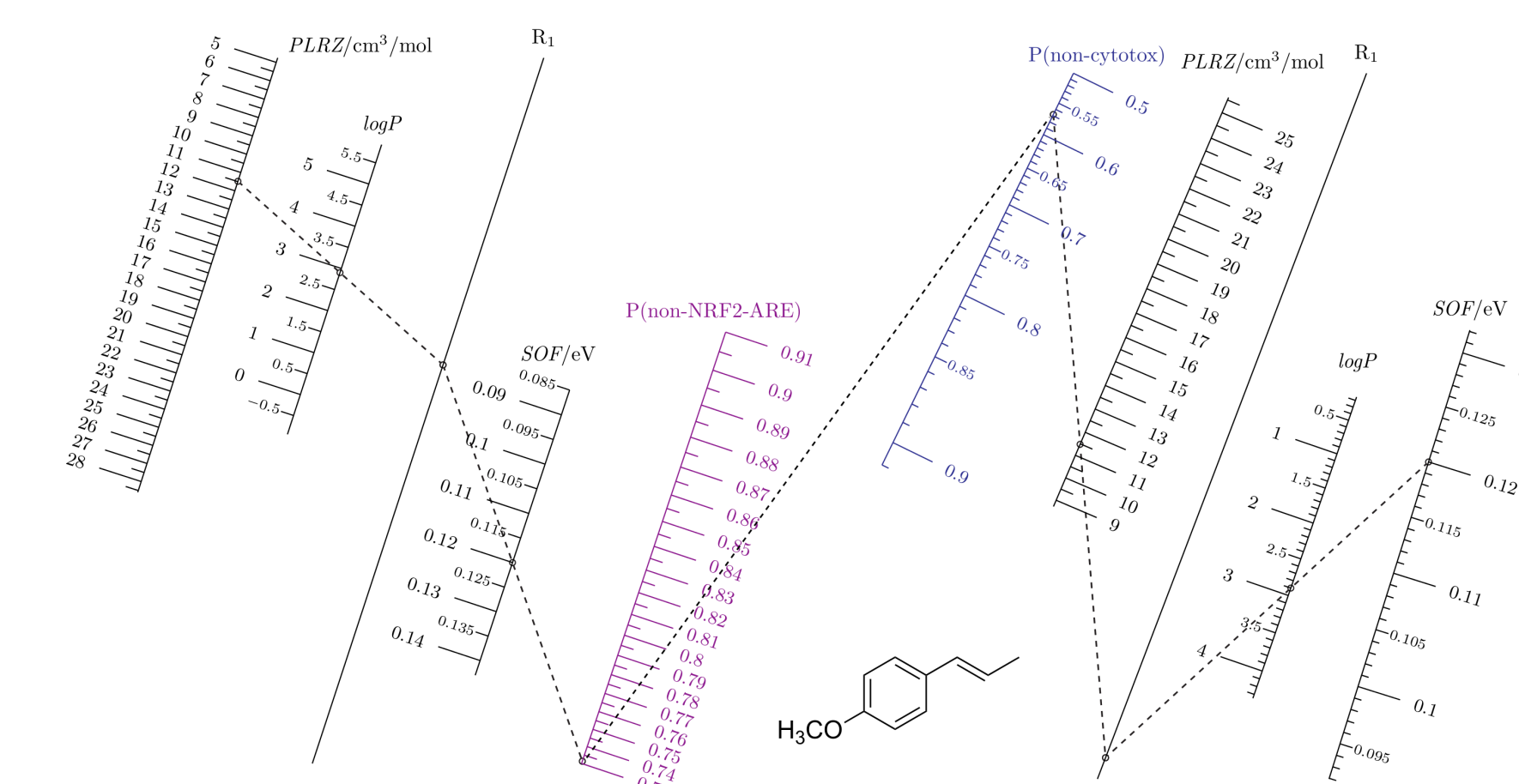
- Model Evaluation

precision = true positive / (true positive + false positive)

recall = true positive / (true positive + 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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