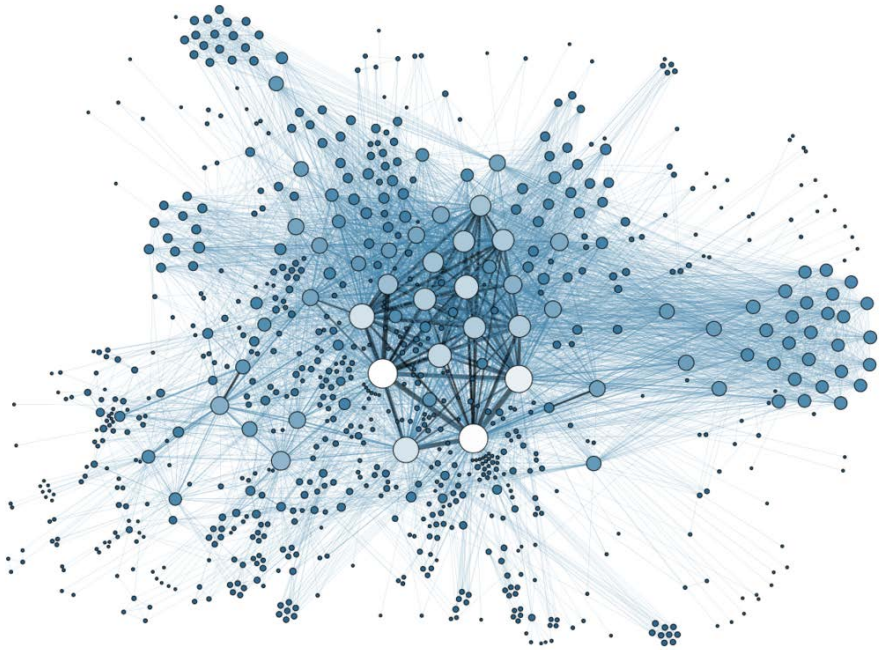

Imran Shah

Computational Systems Biologist

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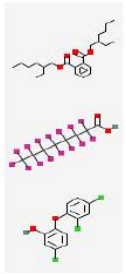
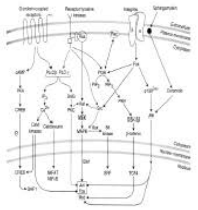
US EPA

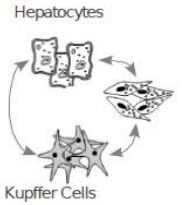
Modelling The Biological Complexity Of Our Environment

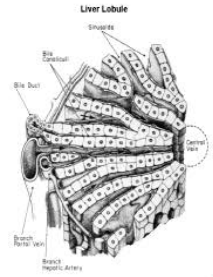
The views expressed in this presentation are those of the author[s] and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

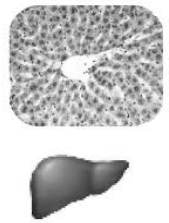
Complex Pathways to Toxicity









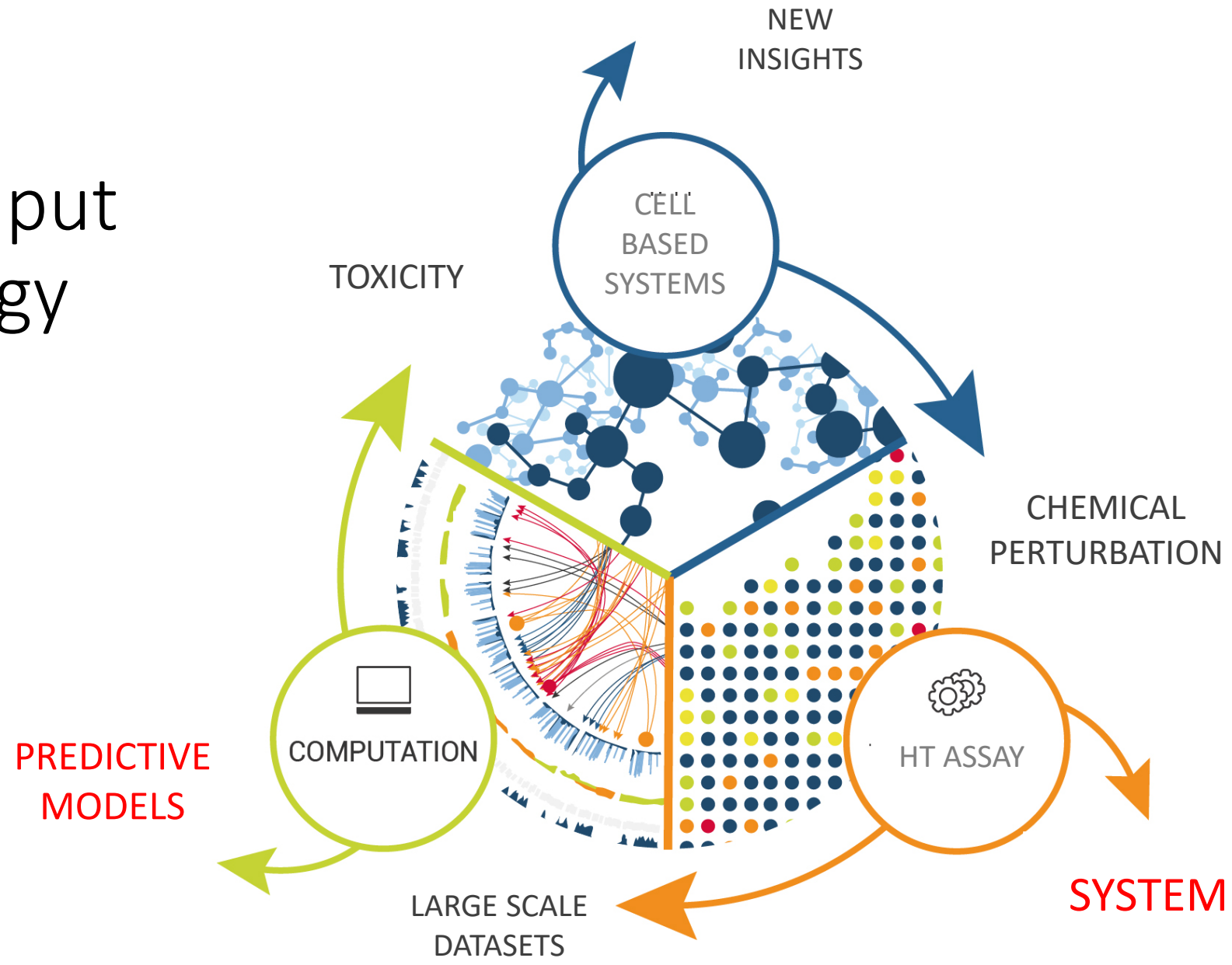


Chemical → Uses → Exposure → Internal Dose ↔ Molecular Changes ↔ Cellular Pathways ↔ Organ Effects ↔ Toxicity

- There are ~ 80,000 chemicals in commerce
- Chemicals are evaluated based on adverse outcomes (derived from animal testing)

- Only ~1000 chemicals have been evaluated systematically via animal testing
- How do we effectively determine the health risks of the remaining thousands of chemicals?

High Throughput Toxicology



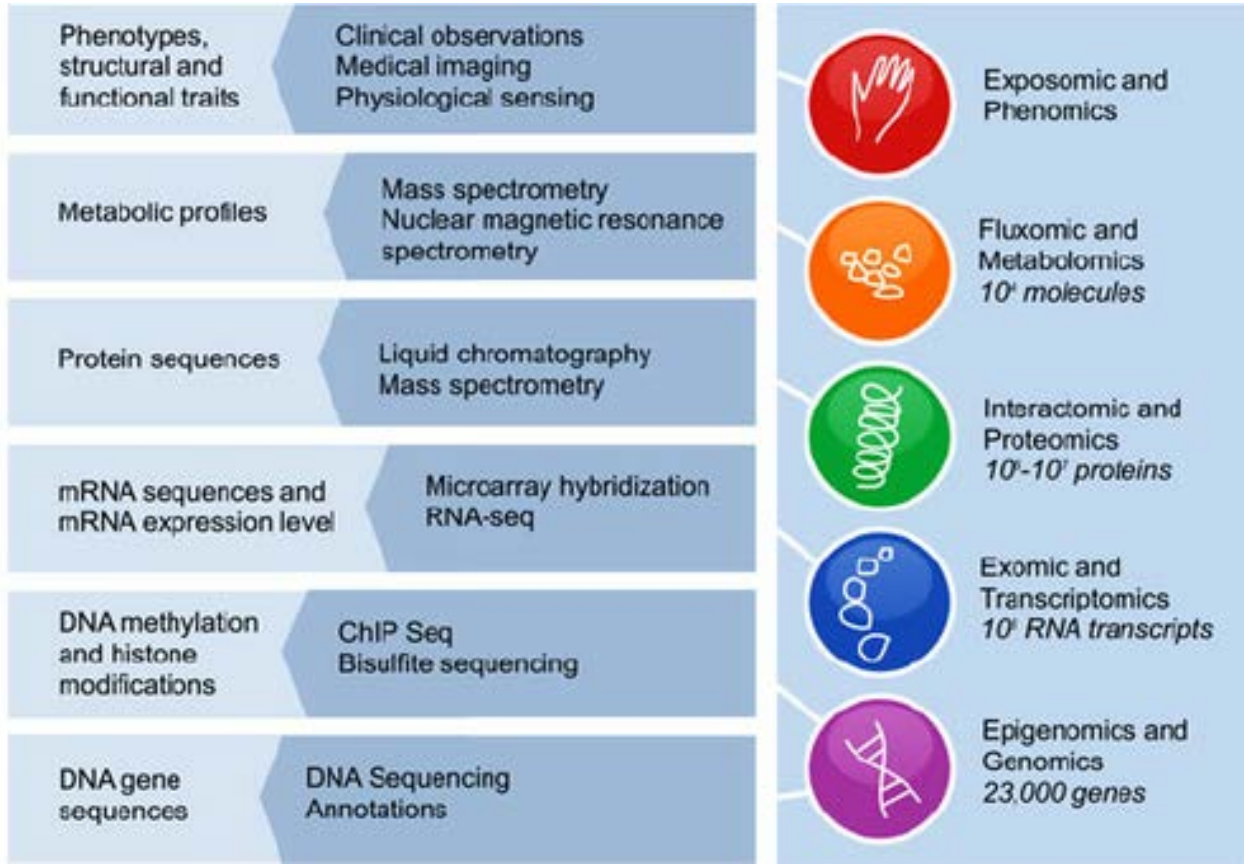
Adapted from ISB

Multiple –*omic* technologies

Varying

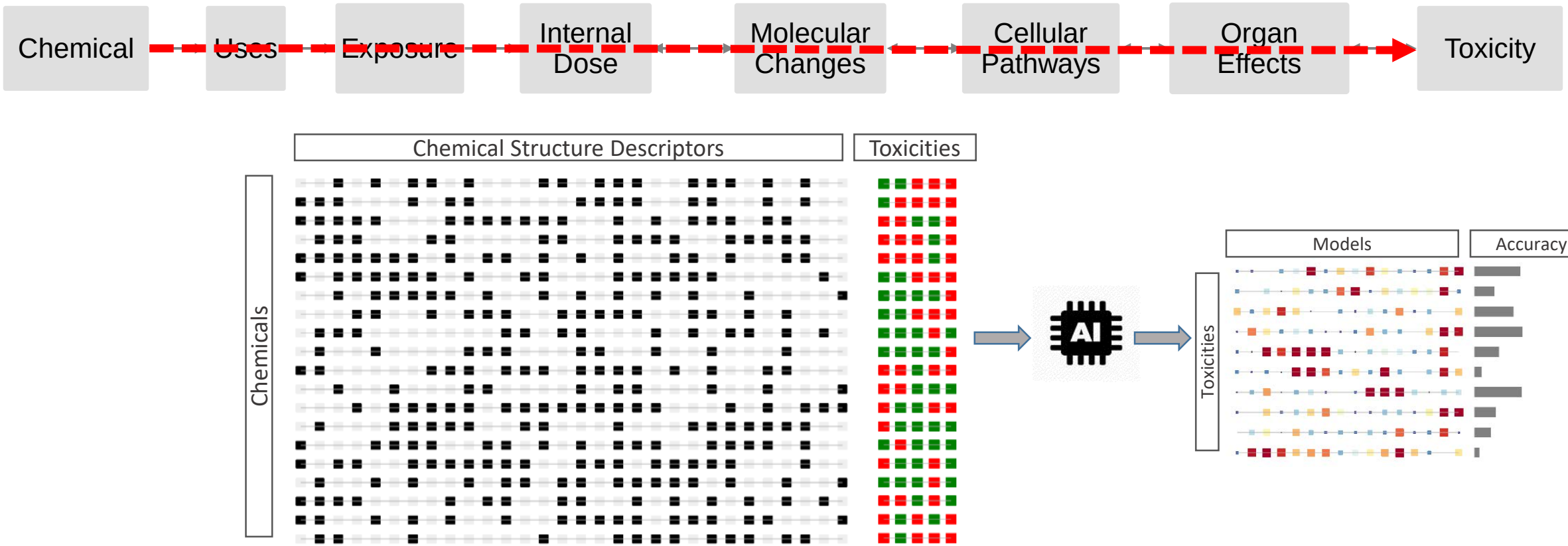
- levels of maturity/acceptance
- biological coverage
- mechanistic value
- translational utility
- cost $$$

High-throughput transcriptomics



DOI: 10.1109/JBHI.2015.2450362

Data-Driven Toxicity Prediction



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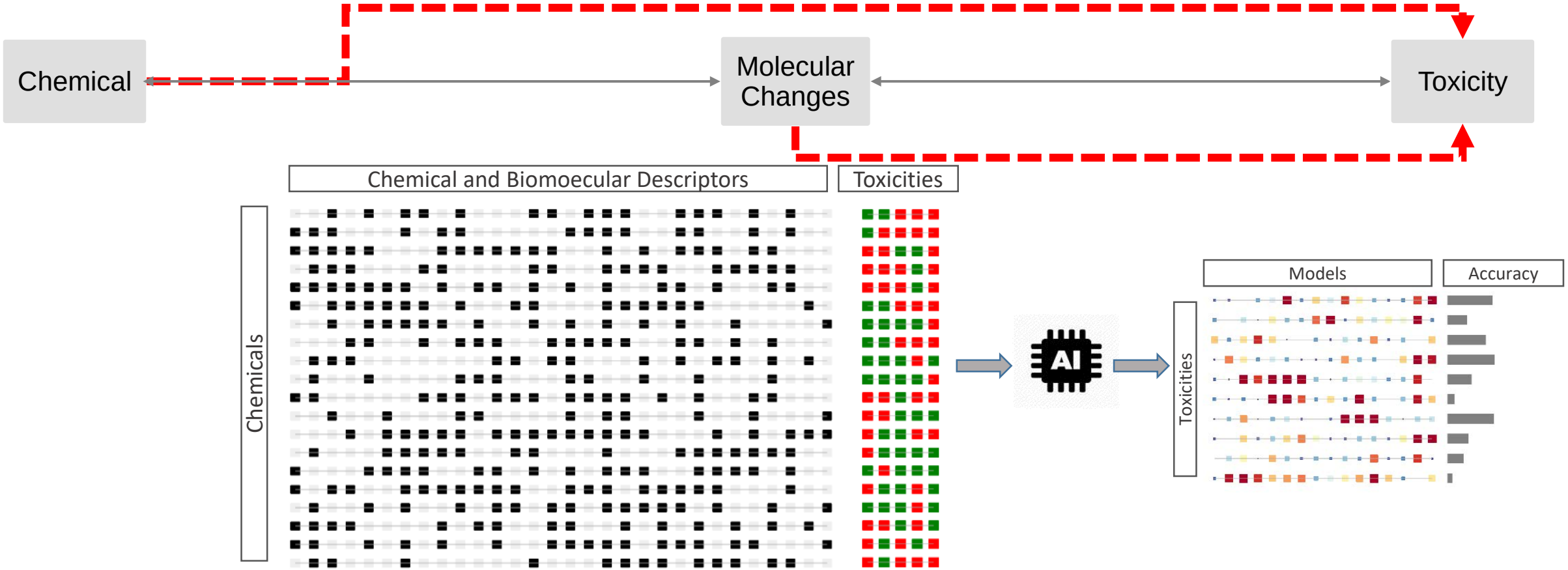
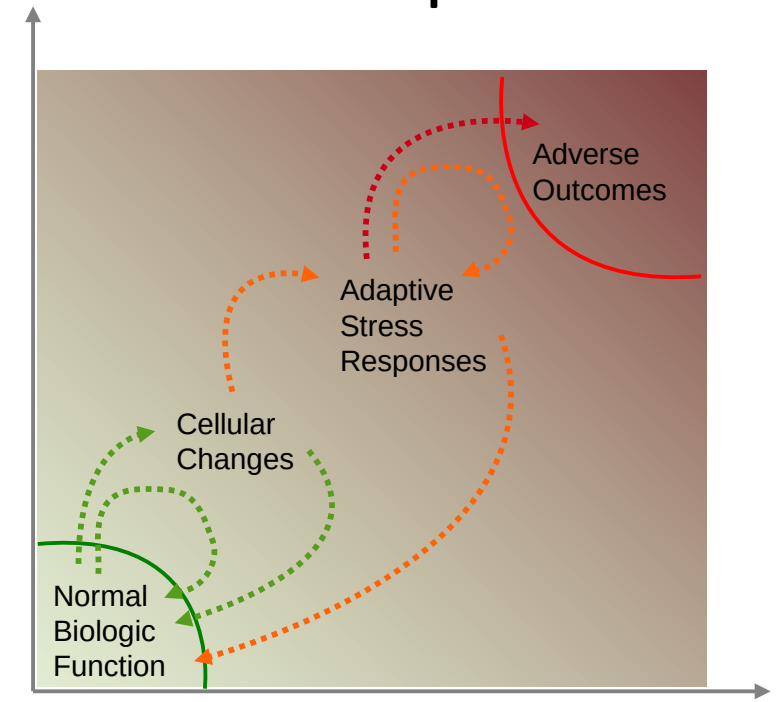
Data-Driven Toxicity Prediction



Liu *et al.* 2017

CAUTION: Large-Scale Data are Complex!

- HTT assays provide a snapshot of system state
- System state (trajectory) can adapt over time and recover or undergo injury
- Analyzing system trajectories reveals “tipping points”
- Tipping points: critical dose-dependent thresholds between adaptation and injury



System Trajectories:

- Some perturbation/ Recovery
- Adaptive stress response/ Recovery
- Adaptive capacity exceeded/ Cell injury/ No recovery

Research

A Section 508–conformant HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1409029.

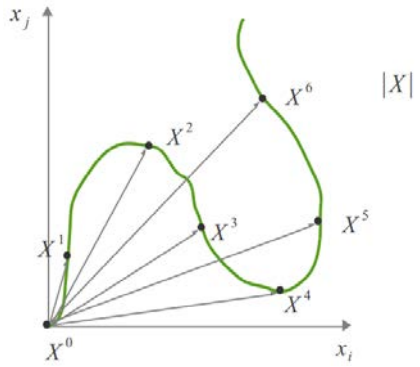
Using ToxCast™ Data to Reconstruct Dynamic Cell State Trajectories and Estimate Toxicological Points of Departure

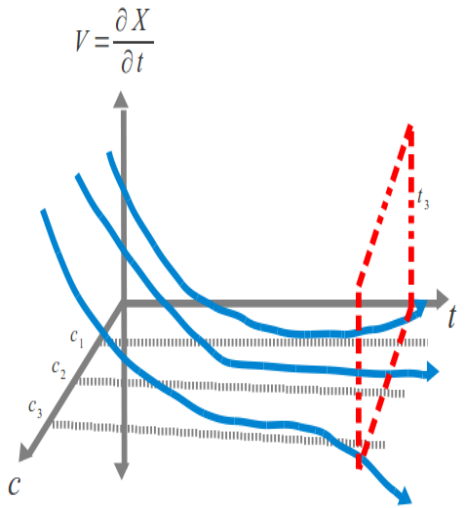
Imran Shah,[1] R. Woodrow Setzer,[1] John Jack,[2] Keith A. Houck,[1] Richard S. Judson,[1] Thomas B. Knudsen,[1] Jie Liu,[3] Matthew T. Martin,[1] David M. Reif,[4] Ann M. Richard,[1] Russell S. Thomas,[1] Kevin M. Crofton,[1] David J. Dix,[1] and Robert J. Kavlock[1]

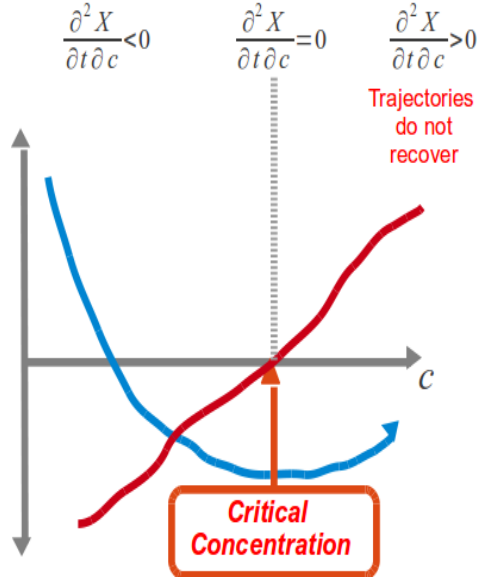
[1]National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA; [2]Department of Statistics, North Carolina State University, Raleigh, North Carolina, USA; [3]Oak Ridge Institute for Science Education (ORISE), U.S. Department of Energy, Oak Ridge, Tennessee, USA; [4]Department of Biological Sciences, North Carolina State University, Raleigh, North Carolina, USA

Shah et al *2016*

Tipping Point in System Recovery







1 Scalar Perturbation

2 Velocity

3 Tipping Point

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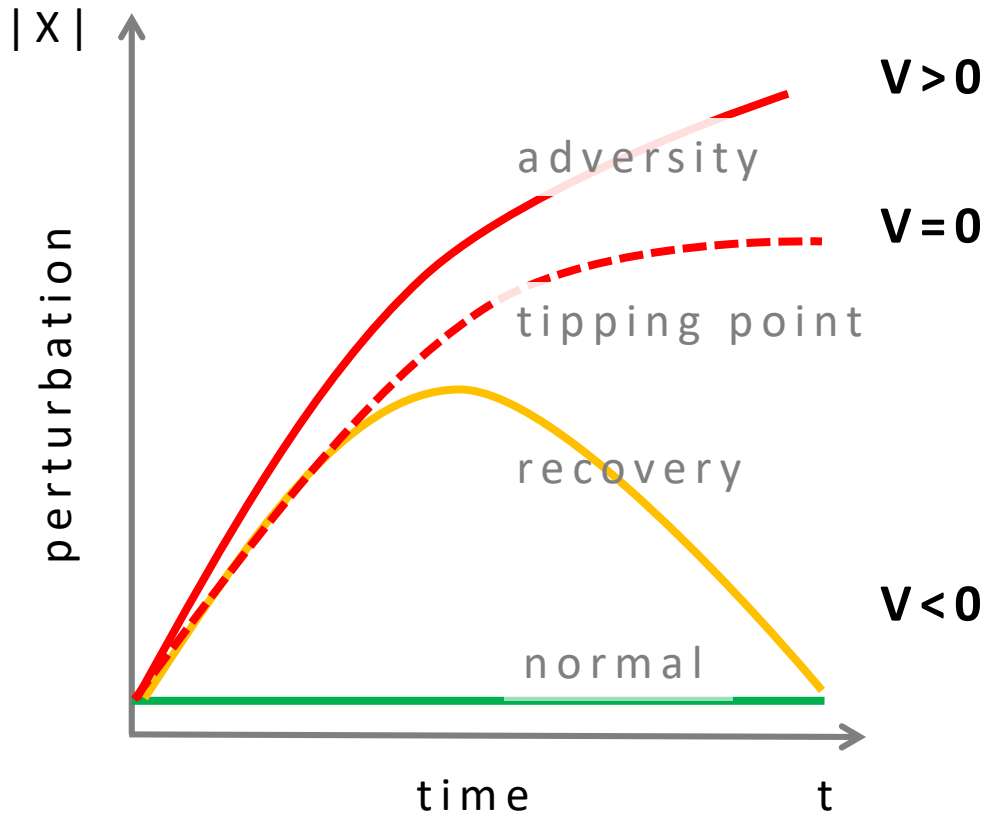
System Trajectories & Tipping Points



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Defining toxicological tipping points in neuronal network development☆

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Summary

- ❑High-throughput data-driven approaches provide alternative toxicity testing strategy
- ❑A broad array of computational predictive approaches can be used to predict chemical-induced effects
- ❑Linking complex disparate data-streams is challenging
- ❑Key issue: How do we differentiate adaptation from adversity *in vitro?*
- ❑Tipping point analysis rigorously identifies critical dose-dependent thresholds in system recovery
- ❑Further experiments underway to evaluate utility

Acknowledgements and Questions

EPA's National Center for Computational Toxicology