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The Physics of Kevin Bacon: Complex Systems and Environmental Science

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The Six Degrees of Kevin Bacon

On the Solvability of the Six Degrees of Kevin Bacon Game

A Faster Graph Diameter and Radius Computation Method

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Abstract. In this paper, we will propose a new algorithm that computes the radius and the diameter of a graph $G = (V, E)$, by finding bounds through heuristics and improving them until exact values can be guaranteed. Although the worst-case running time is $\mathcal{O}(|V| \cdot |E|)$, we will experimentally show that, in the case of real-world networks, it performs much better, finding the correct radius and diameter value after 10–100 BFSes instead of $|V|$ BFSes (independent of the value of $|V|$), and thus having running time $\mathcal{O}(|E|)$. Apart from efficiency, compared to other similar methods, the one proposed in this paper has three other advantages. It is more robust (even in the worst cases, the number of BFSes performed is not very high), it is able to simultaneously compute radius and diameter (halving the total running time whenever both values are needed), and it works both on directed and undirected graphs with very few modifications. As an application example, we use our new algorithm in order to determine the solvability over time of the "six degrees of Kevin Bacon" game.

1 Introduction

The six degrees of separation game is a trivia game which has been inspired by the well-known social experiment of Stanley Milgram [11], which was in turn a continuation of the empirical study of the structure of social networks by Michael Gurevich [7]. Indeed, the notion of six degrees of separation has been formulated for the first time by Frigyes Karinthy in 1929, who conjectured that any two individuals can be connected through at most five acquaintances. This conjecture has somehow been experimentally verified by Milgram and extremely popularized by a theater play of John Guare, successively adapted to the cinema by Fred Schepisi. The corresponding game refers to a social network, such as the

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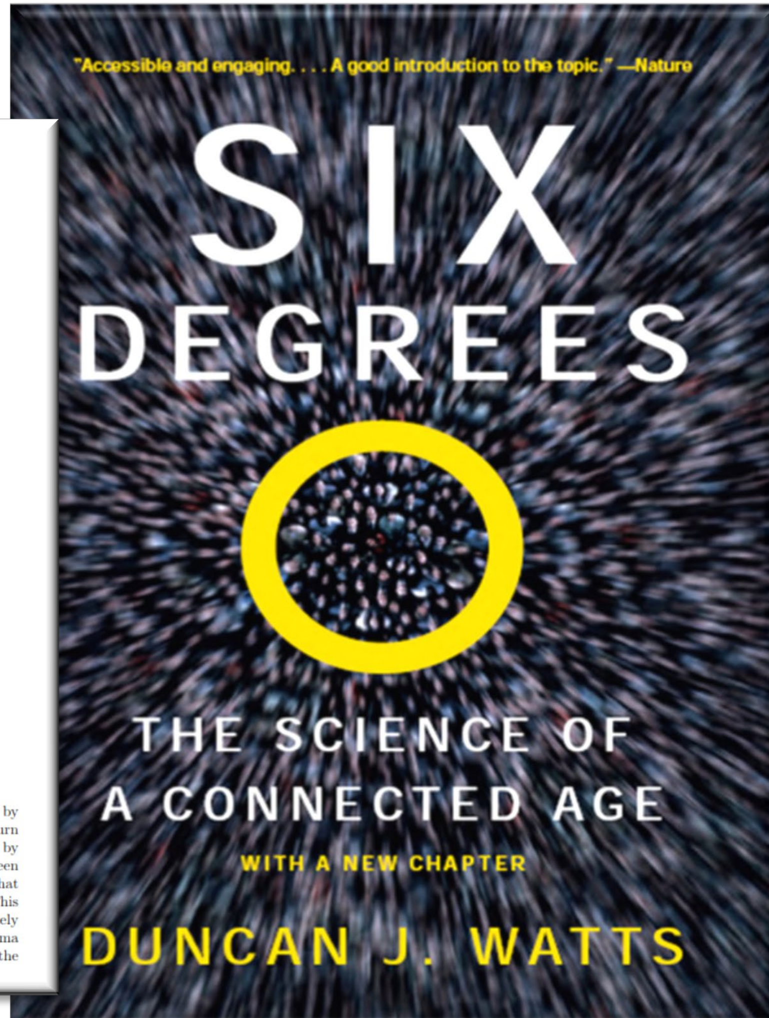

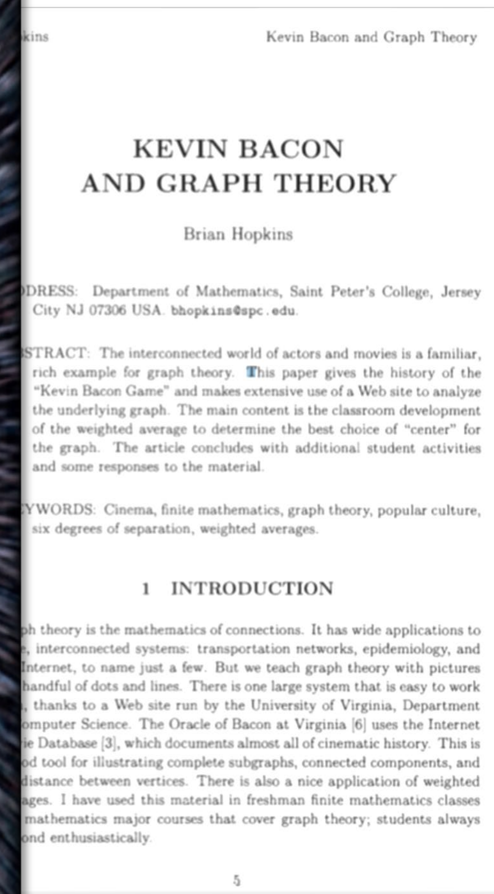

KEVIN BACON AND GRAPH THEORY

Brian Hopkins

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STRACT: The interconnected world of actors and movies is a familiar, rich example for graph theory. This paper gives the history of the "Kevin Bacon Game" and makes extensive use of a Web site to analyze the underlying graph. The main content is the classroom development of the weighted average to determine the best choice of "center" for the graph. The article concludes with additional student activities and some responses to the material.

YWORDS: Cinema, finite mathematics, graph theory, popular culture, six degrees of separation, weighted averages.

1 INTRODUCTION

ph theory is the mathematics of connections. It has wide applications to , interconnected systems: transportation networks, epidemiology, and Internet, to name just a few. But we teach graph theory with pictures handful of dots and lines. There is one large system that is easy to work , thanks to a Web site run by the University of Virginia, Department omputer Science. The Oracle of Bacon at Virginia [6] uses the Internet ie Database [3], which documents almost all of cinematic history. This is od tool for illustrating complete subgraphs, connected components, and distance between vertices. There is also a nice application of weighted ages. I have used this material in freshman finite mathematics classes mathematics major courses that cover graph theory; students always ond enthusiastically.

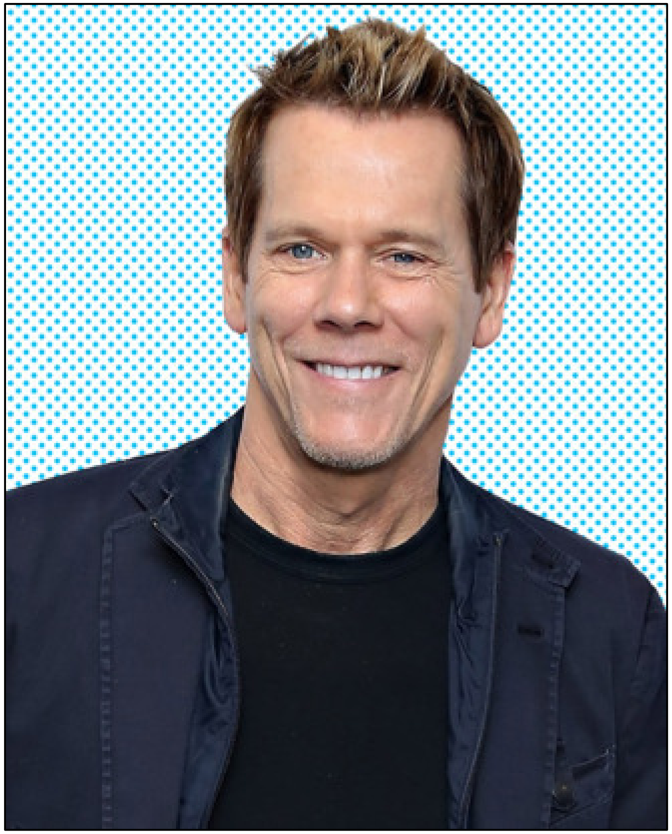
Kevin Bacon

1978

1984

1992

1995



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Michael B. Jordan

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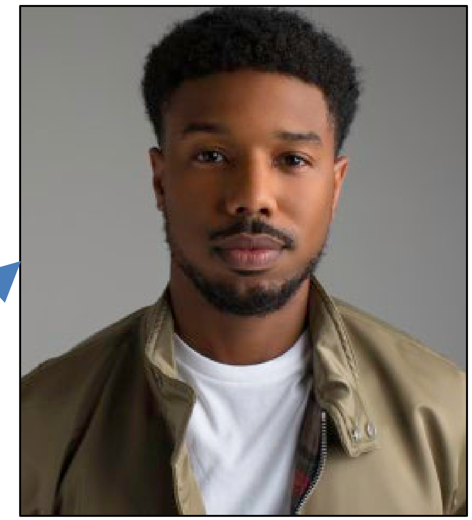
Connectedness to Michael B. Jordan

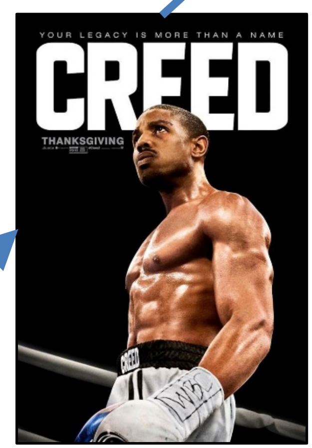
Frances McDormand
Best Actress Winner 2018

Hail Caesar
McDormand &
Channing Tatum

GI Joe: Retaliation
Tatum & Bruce Willis



Expendables
Willis &
Sylvester Stallone



Creed
Stallone & Jordan

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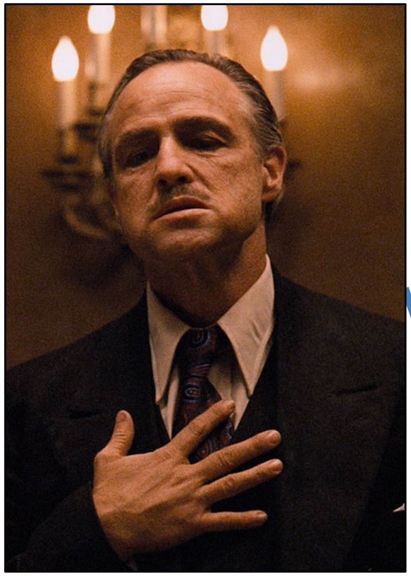
Connectedness to Michael B. Jordan

Avengers: Infinity War
Paltrow & Chadwick Boseman

Black Panther
Boseman & Jordan



Marlon Brando
Best Actor 1954 and 1972
Died 2004

Superman
with Gene Hackman

The Royal Tenenbaums
Hackman & Gwyneth Paltrow

Small World Networks

United States Environmental Protection Agency

Watts and Strogatz (1998)

letters to nature

Collective dynamics of 'small-world' networks

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Networks of coupled dynamical systems have been used to model biological oscillators, Josephson junction arrays, excitable media, neural networks, spatial games, genetic control networks and many other self-organizing systems. Ordinarily, the connection topology is assumed to be either completely regular or completely random. But many biological, technological and social networks lie somewhere between these two extremes. Here we explore simple models of networks that can be tuned through this middle ground: regular networks 'rewired' to introduce increasing amounts of disorder. We find that these systems can be highly clustered, like regular lattices, yet have small characteristic path lengths, like random graphs. We call them 'small-world' networks, by analogy with the small-world phenomenon (popularly known as six degrees of separation). The neural network of the worm Caenorhabditis elegans, the power grid of the western United States, and the collaboration graph of film actors are shown to be small-world networks. Models of dynamical systems with small-world coupling display enhanced signal-propagation speed, computational power, and synchronizability. In particular, infectious diseases spread more easily in small-world networks than in regular lattices.

Travers and Milgram (1969):

296 arbitrary individuals in Nebraska and Boston were asked to give a letter to an acquaintance most likely to help it reach a target person in Massachusetts. 64 reached the target person, average number of intermediaries was 5.2

Collins and Chow (1998)

news and views

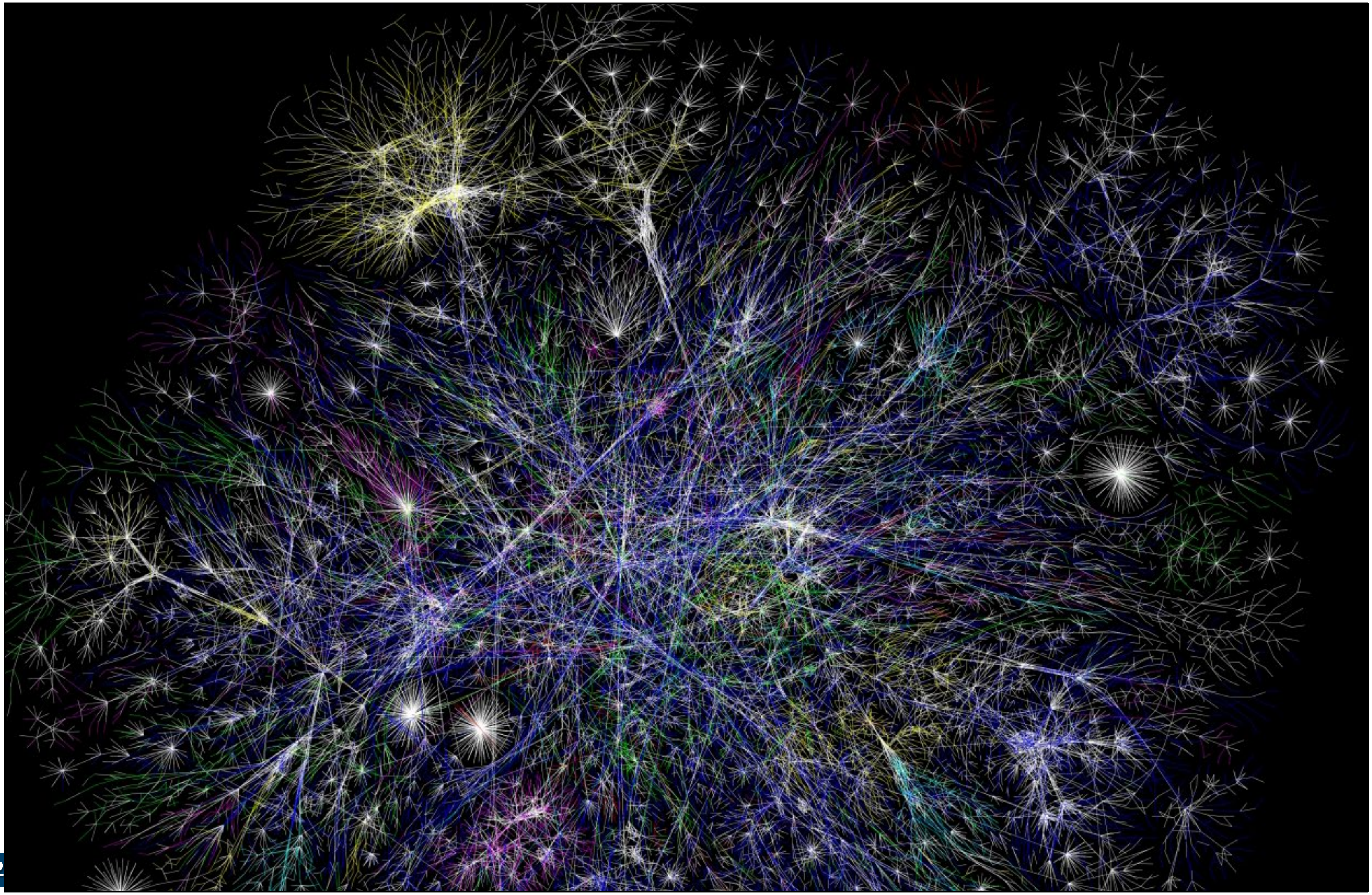
It's a small world

James J. Collins and Carson C. Chow

The concept of Six Degrees of Separation has been formalized in so-called 'small-world networks'. The principles involved could be of use in settings as diverse as improving networks of cellular phones and understanding the spread of infections.

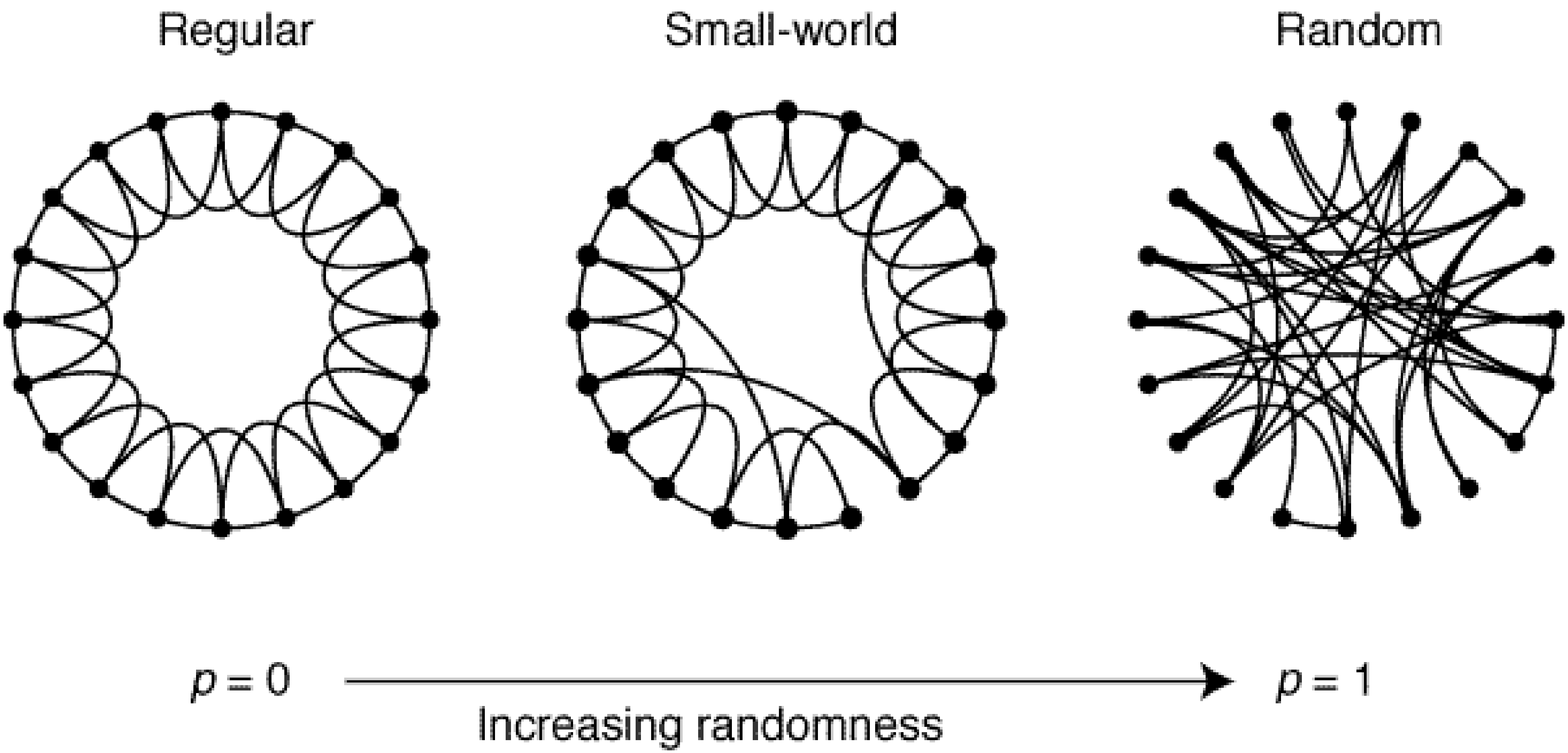
Figure 1 Three degrees. Because Kevin Bacon has appeared in many films, most actors have low Bacon numbers and the game Six Degrees of Kevin Bacon has declined in popularity. It is possible to centre the game around a newer star such as Leonardo DiCaprio. These film stills, running clockwise, show that in this case there are at most three degrees of separation between DiCaprio and Helena Bonham-Carter, through Kate Winslet (Titanic, Columbia TriStar; Sense and Sensibility, Columbia TriStar), Emma Thompson (Sense and Sensibility; Much Ado About Nothing, Entertainment Films) and Kenneth Branagh (Much Ado About Nothing; Frankenstein; Columbia TriStar). Short cuts between cliques could be created in this game through some of DiCaprio's well-connected co-stars such as Sharon Stone (The Quick and the Dead; TriStar; not shown).

The Internet (Circa 2005)



https://upload.wikimedia.org/wikipedia/commons/d/d2/Internet_map_1024.jpg

Complex is Not the Same as Random



Watts and Strogatz (1998)

Chemical Regulation in the United States

- Park *et al.* (2012): At least 3221 chemical signatures in pooled human blood samples, many appear to be exogenous
- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)
- Different testing requirements exist for food additives, pharmaceuticals, and pesticide active ingredients (NRC, 2007)

November 29, 2014

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Chemical Regulation in the United States

- Most other chemicals, ranging from industrial waste to dyes to packing materials, are covered by the Toxic Substances Control Act (TSCA)
  - Thousands of chemicals on the market were either “grandfathered” in or were allowed without experimental assessment of hazard, toxicokinetics, or exposure
  - Thousands of new chemical use submissions are made to the EPA every year
- TSCA was updated in June, 2016 to allow evaluation of these and other chemicals
  - Methods are being developed to prioritize these existing and new chemicals for testing

November 29, 2014

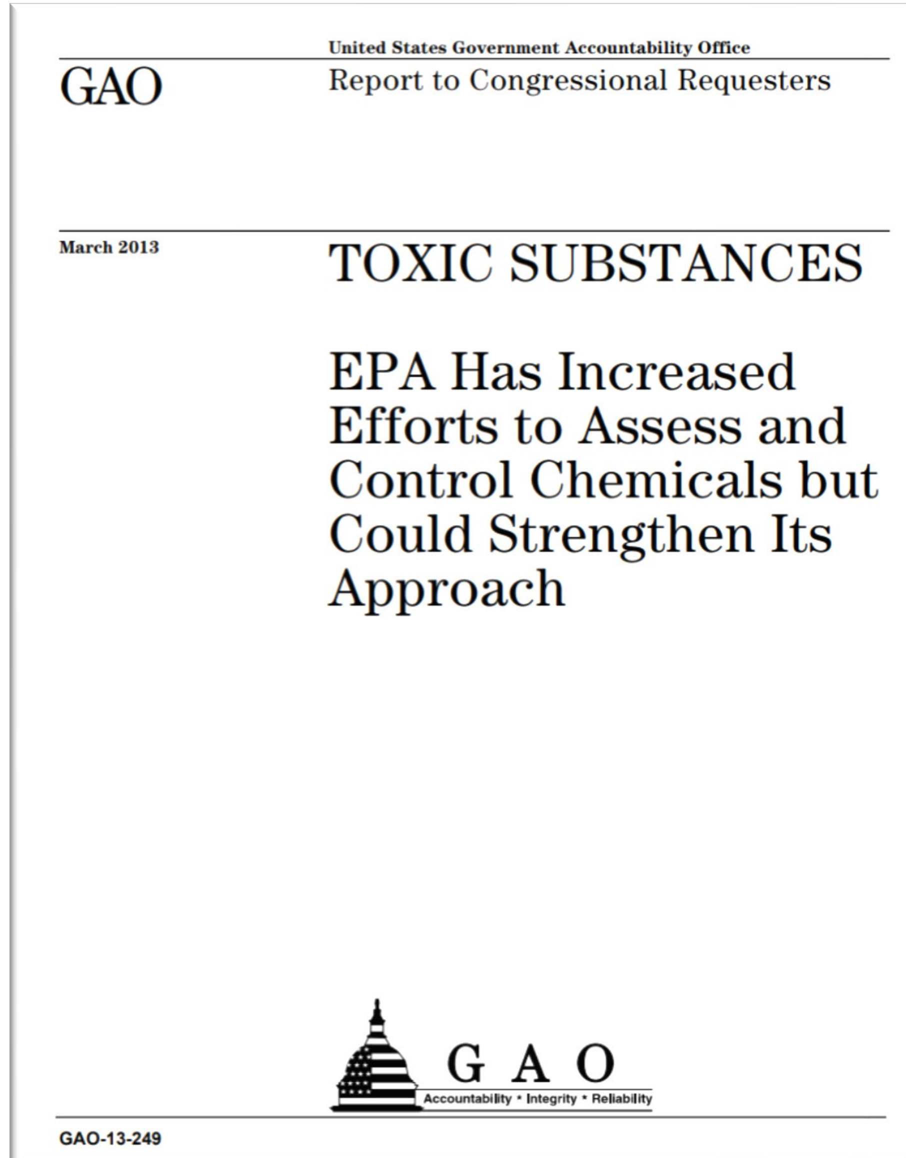
Chemical Regulation in the United States

United States Environmental Protection Agency

"Of the thousands of chemicals listed for commercial use in the United States, EPA has used its authority to limit or ban five chemicals since TSCA was enacted."

TSCA was updated in June, 2016 to allow more rapid evaluation of chemicals

- Methods are being developed to prioritize these existing and new chemicals for testing


United States Government Accountability Office

GAO Report to Congressional Requesters

March 2013

TOXIC SUBSTANCES

EPA Has Increased Efforts to Assess and Control Chemicals but Could Strengthen Its Approach

GAO
Accountability • Integrity • Reliability

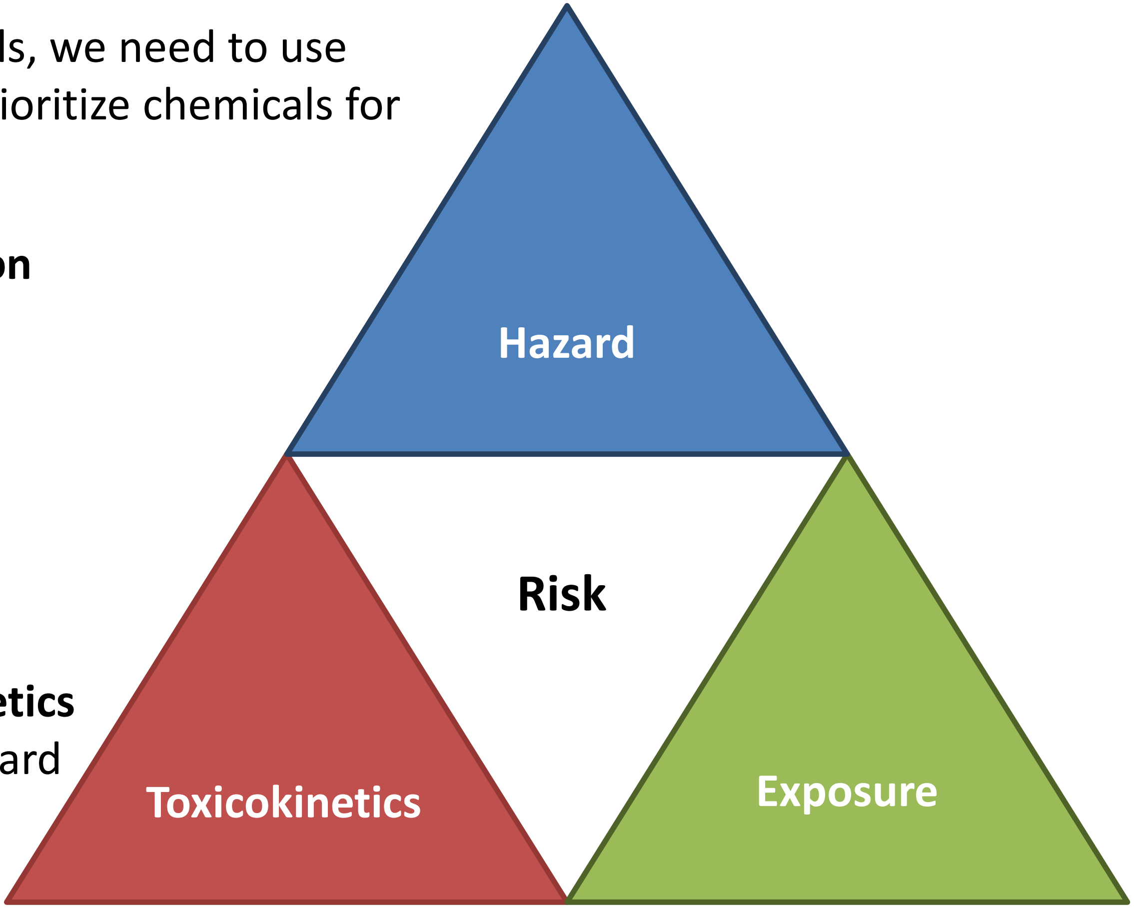
GAO-13-249

Chemical Risk = Hazard x Exposure

- National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure

- To address thousands of chemicals, we need to use "high throughput methods" to prioritize chemicals for additional study

- **High throughput risk prioritization** needs:
    1. high throughput **hazard** characterization (from HTT project)
    2. high throughput **exposure** forecasts
    3. high throughput **toxicokinetics** (*i.e.*, dosimetry) linking hazard and exposure



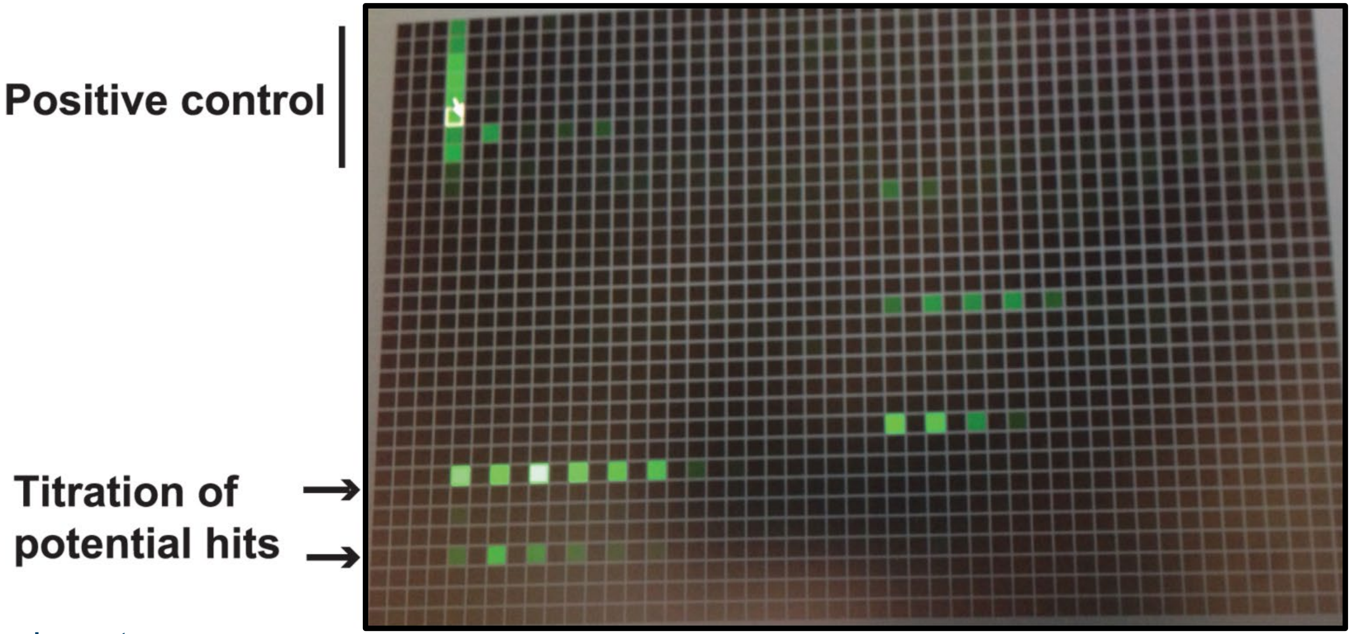
High-throughput Screening for Chemical Hazard

Hertzberg and Pope (2000):

- "New technologies in high-throughput screening have significantly increased throughput and reduced assay volumes"

- "Key advances over the past few years include new fluorescence methods, detection platforms and liquid-handling technologies."

Kaewkhaw et al. (2016)



High-Throughput Testing of Chemicals

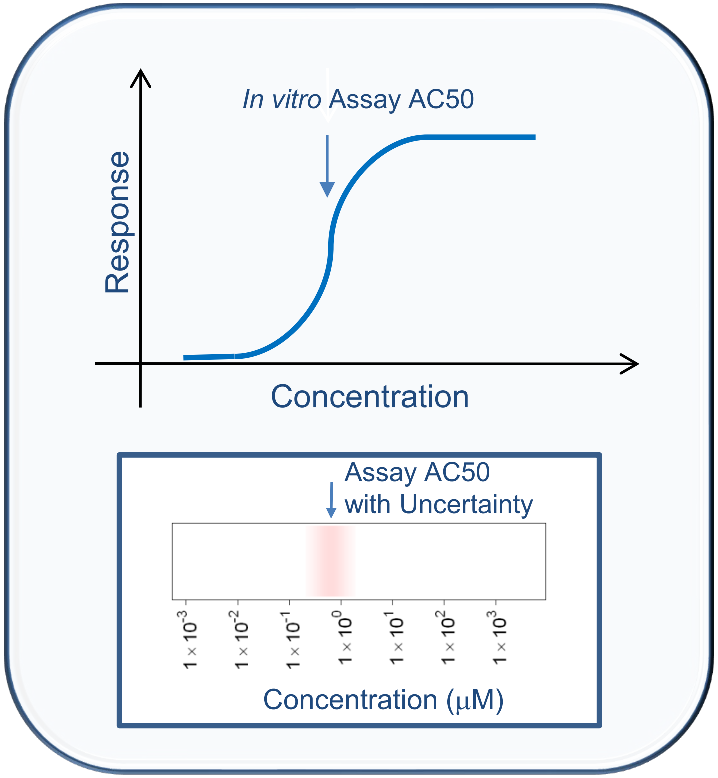
- We might estimate points of departure *in vitro* using high throughput screening (HTS)

- **Tox21**: Examining >8,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)

- **ToxCast**: For a subset (>2000) of Tox21 chemicals ran >1100 additional assays (Kavlock *et al.*, 2012)

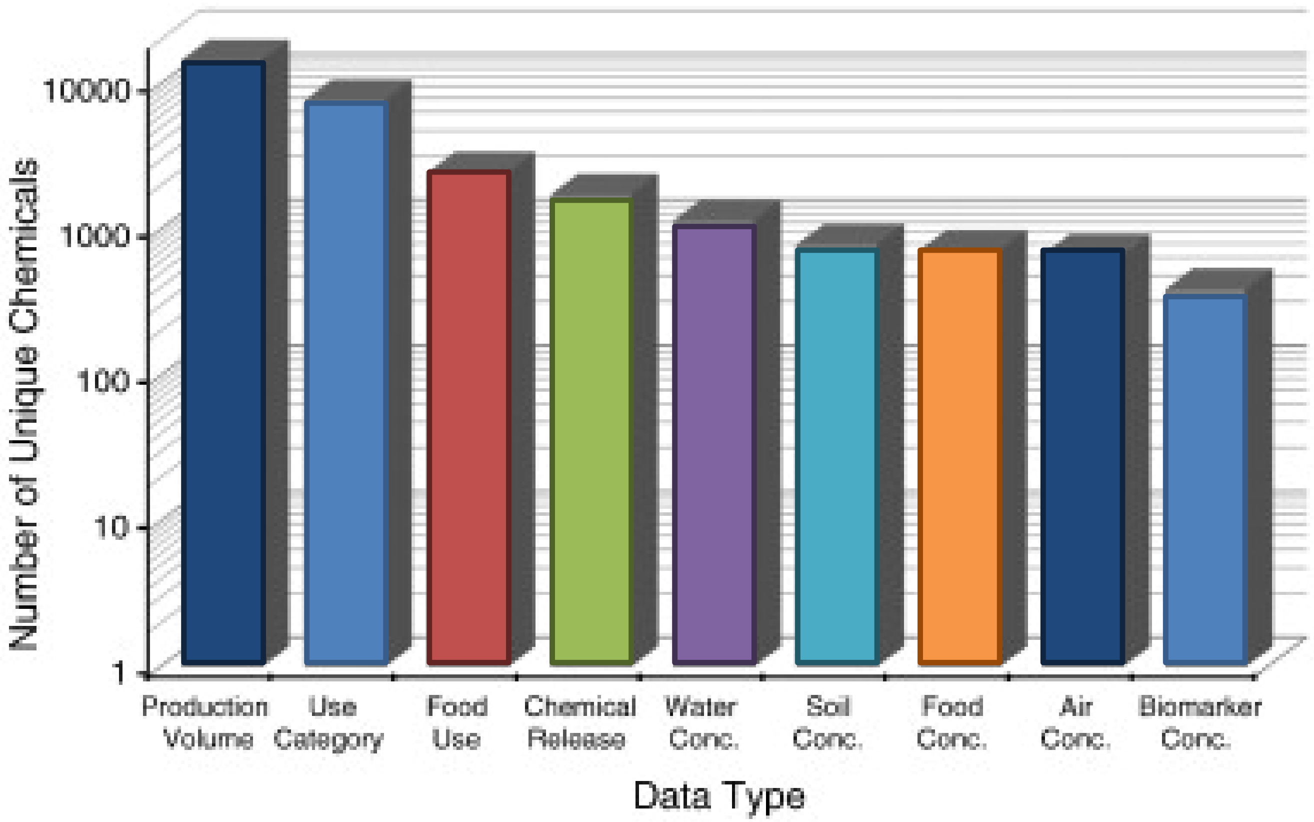
- Most assays conducted in dose-response format (identify 50% activity concentration – AC50 – and efficacy if data described by a Hill function, Filer *et al.*, 2016)

- All data are public: http://comptox.epa.gov/dashboard/



Limited Available Data for Exposure Estimation

Most chemicals lack public exposure-related data beyond production volume (Egeghy et al., 2012)



Exposure is a Complex Problem

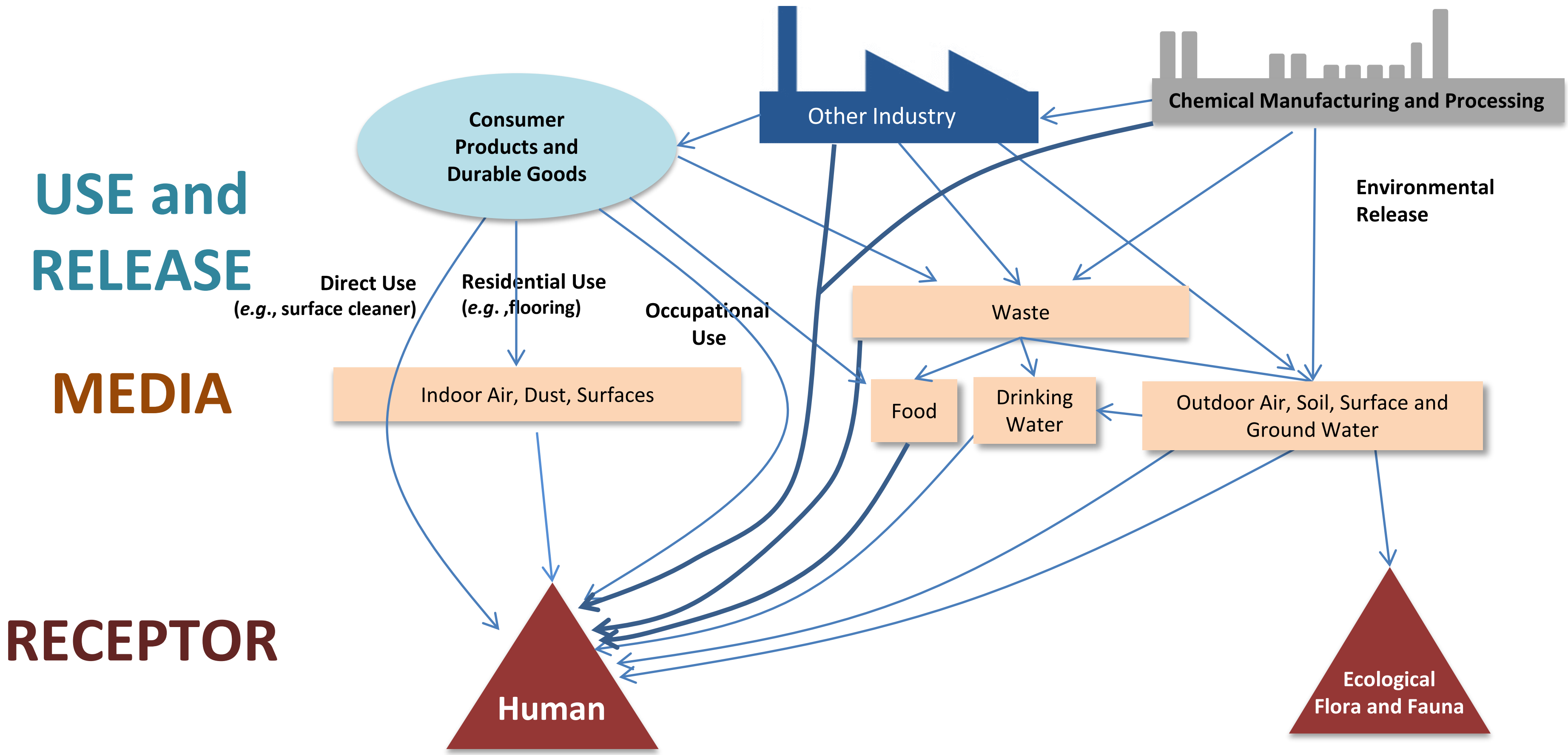


Figure from Kristin Isaacs

Exposure is a Complex Problem

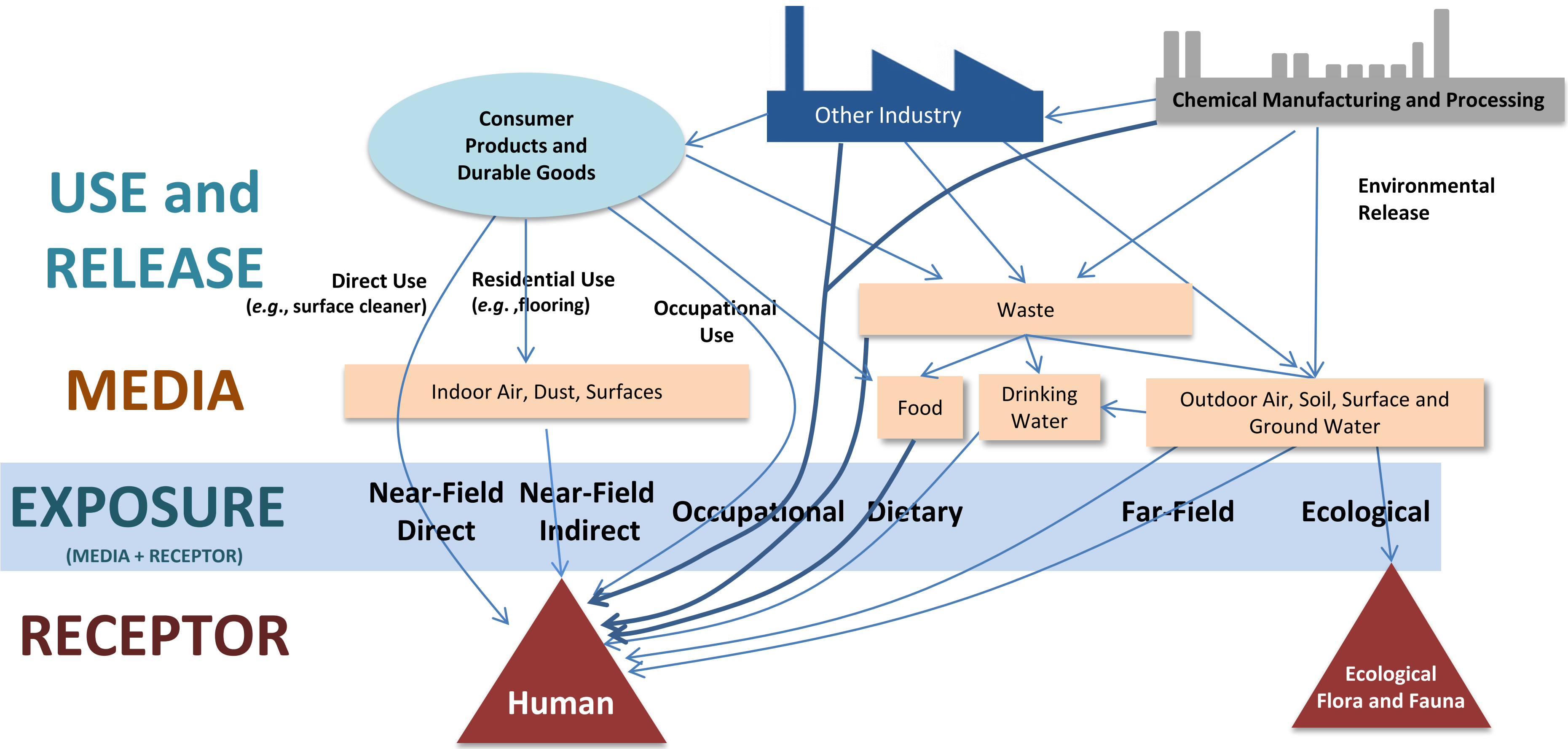


Figure from Kristin Isaacs

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The Exposure Event is Often Unobservable

- The exposure pathway is the actual interaction of the receptor and media, e.g. consuming potato chips

- For humans in particular, these events are often unobserved and for many reasons (including ethics and privacy) may remain unobservable

  - *Did you eat the serving size or the whole bag of potato chips?*

- **Either predict** exposure using data and models up-stream of the exposure event

- **Or infer** exposure pathways from down-stream data, especially biomarkers of exposure

Figure modified from original by Kristin Isaacs

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What Do We Know About Exposure?

Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) provides an important tool for monitoring public health

Large, ongoing CDC survey of US population: demographic, body measures, medical exam, biomonitoring (health and exposure), …

Designed to be representative of US population according to census data

Data sets publicly available (http://www.cdc.gov/nchs/nhanes.htm)

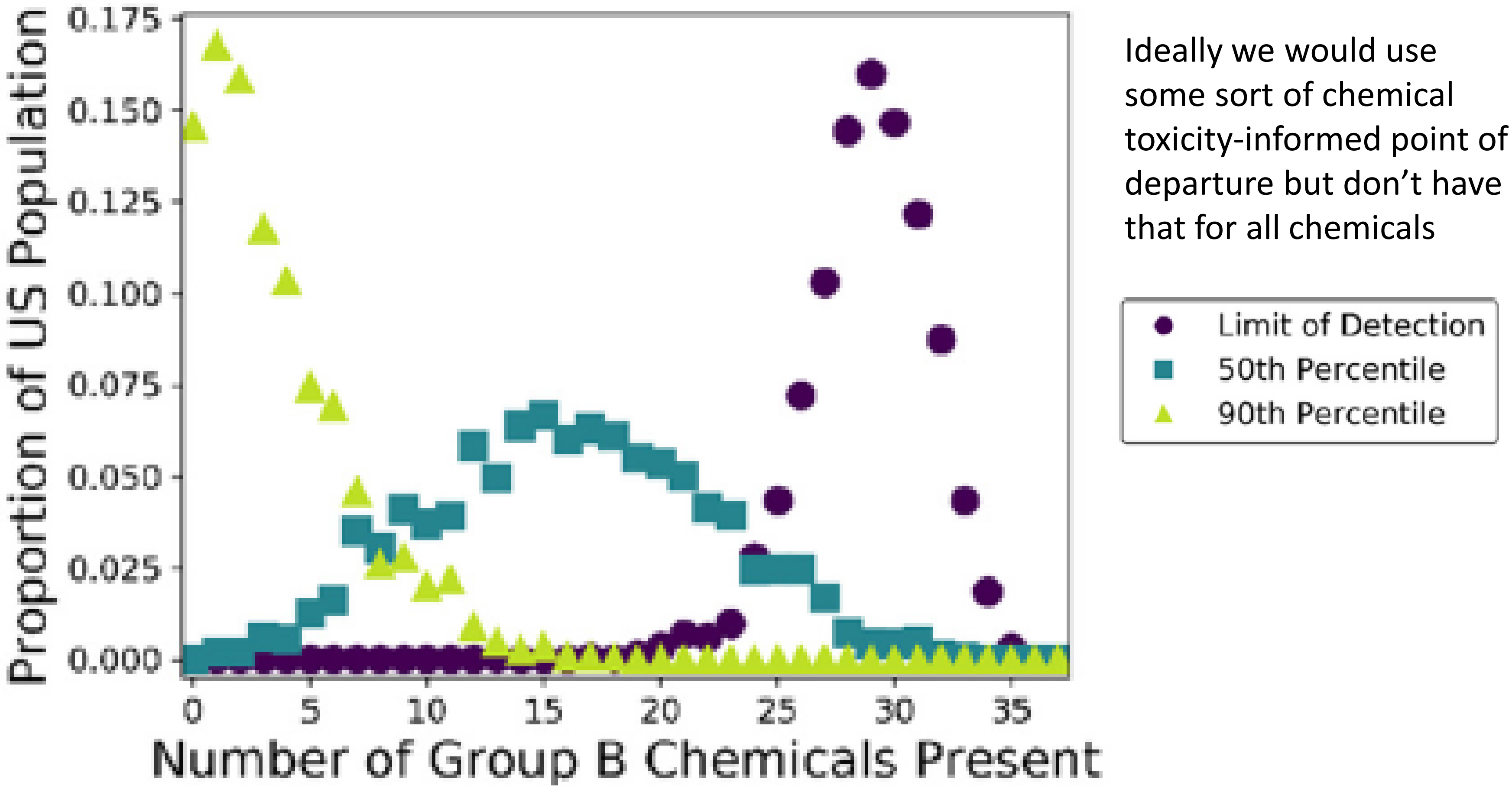
Includes measurements of:

- Body weight
- Height
- **Chemical analysis of blood and urine**

nhanes
National Health and Nutrition Examination Survey

Co-Occurrence of Chemicals in Individuals

The number of chemicals (out of 37) "present" in individuals depends upon where you set the limit



Ideally we would use some sort of chemical toxicity-informed point of departure but don't have that for all chemicals

Kapraun et al. (2017)

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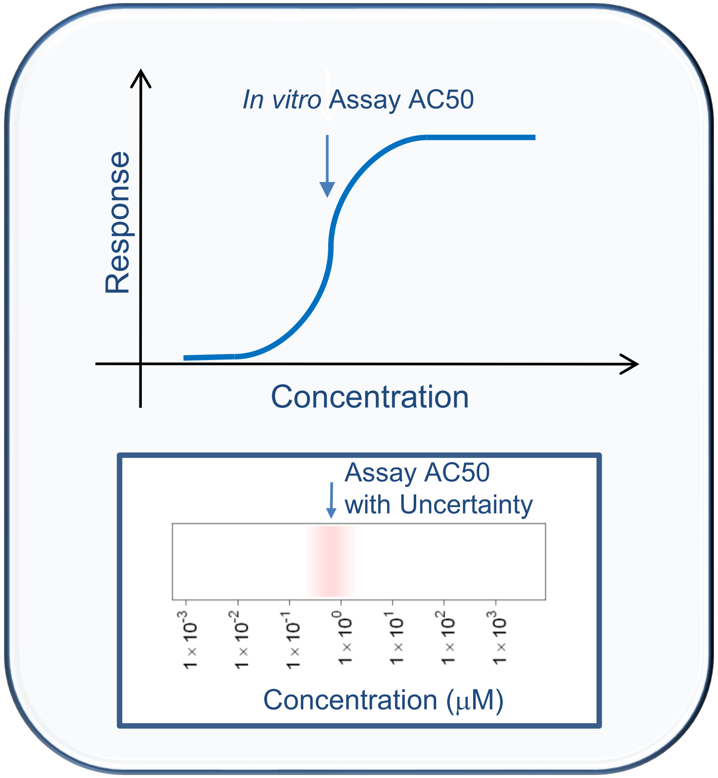
High-Throughput Testing of Chemicals

37 chemicals means 2^{37} combinations that's 134,217,728 combinations – Tox21 has tested ~8000 chemicals over the last ten years



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High-Throughput Testing of Chemicals

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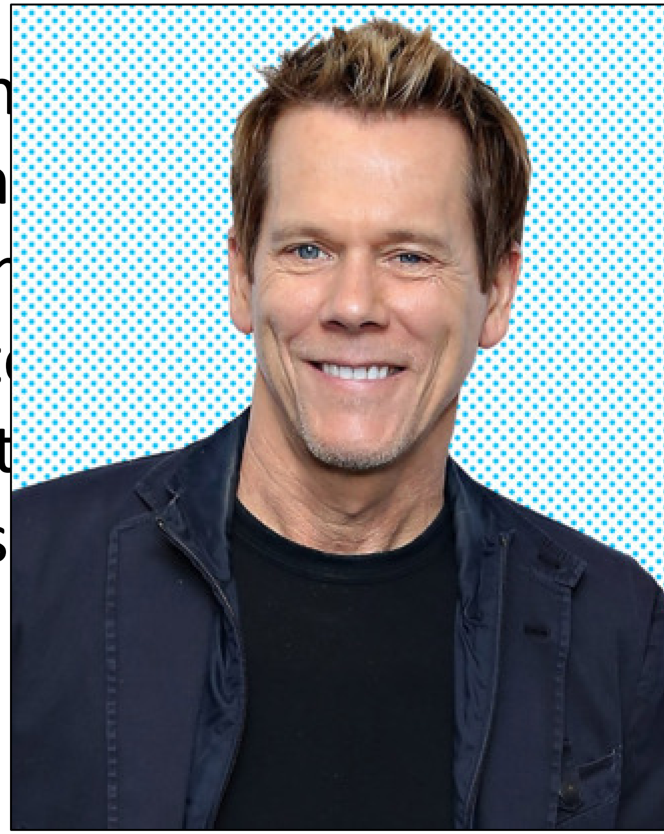
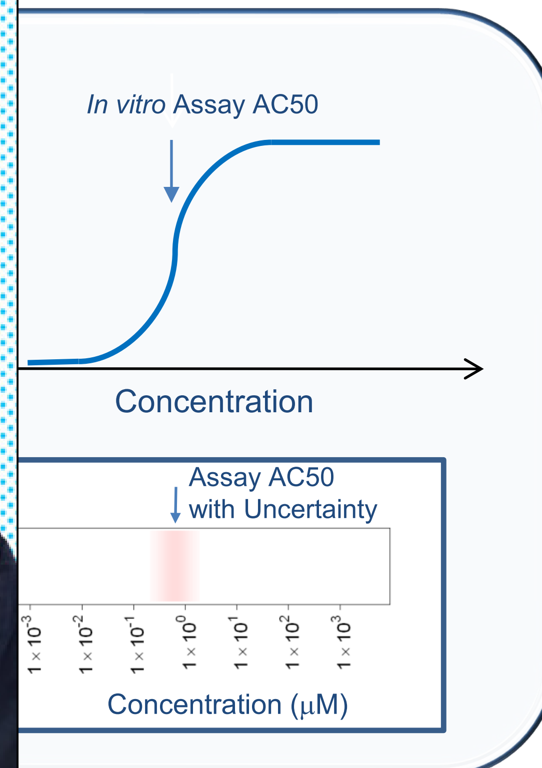




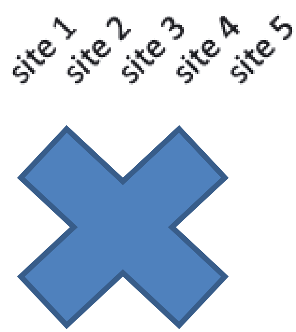
The Structure of Chemical Exposure

finch species

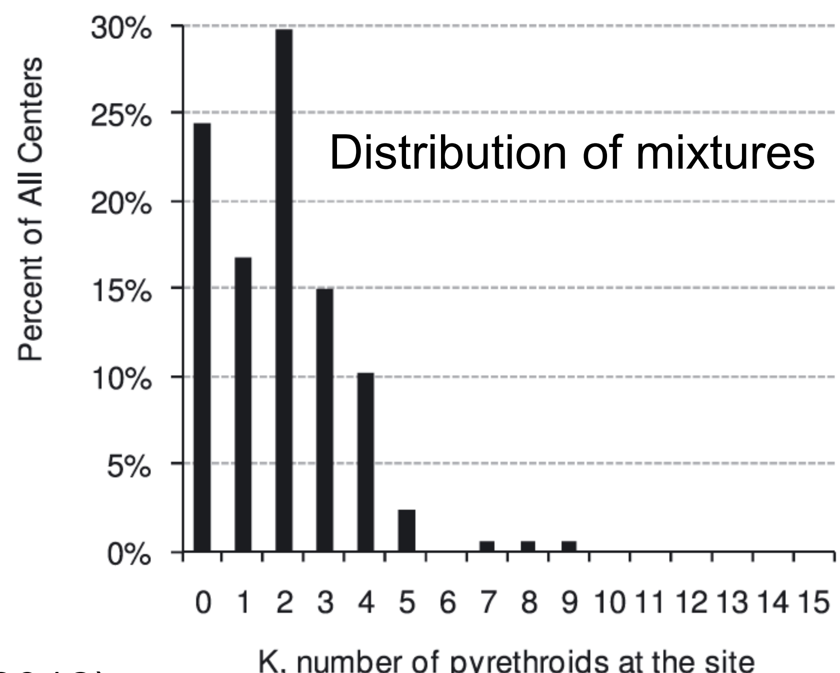
Loxigilla noxis
Melanospiza richardson
Tiara olivacea
Tiara bicolor
Tiara canora
Loxipasser anoxanthus

chemical species

chemical 1
chemical 2
chemical 3
chemical 4
chemical 5
chemical 6



- For **n** chemicals **2^n** combinations are possible
  - However, not all are observed
- Diamond (1975): Not all finch species present on all islands of Caribbean
- Tornero-Velez et al. (2012): Not all chemical combinations present at all sites



Tornero-Velez et al. (2012)

Frequent Itemset Mining (FIM)

- Frequent itemset mining (FIM, Borgelt, 2012) identifies the prevalence (probability from 0-100%) that a set of items that co-occur in a "transaction"

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Frequent Itemset Mining (FIM)

- Frequent itemset mining (FIM, Borgelt, 2012) identifies the prevalence (probability from 0-100%) that a set of items that co-occur in a “transaction”

- Between 5pm and 7pm, customers tended to co-purchase beer and diapers

Identifying Prevalent Mixtures

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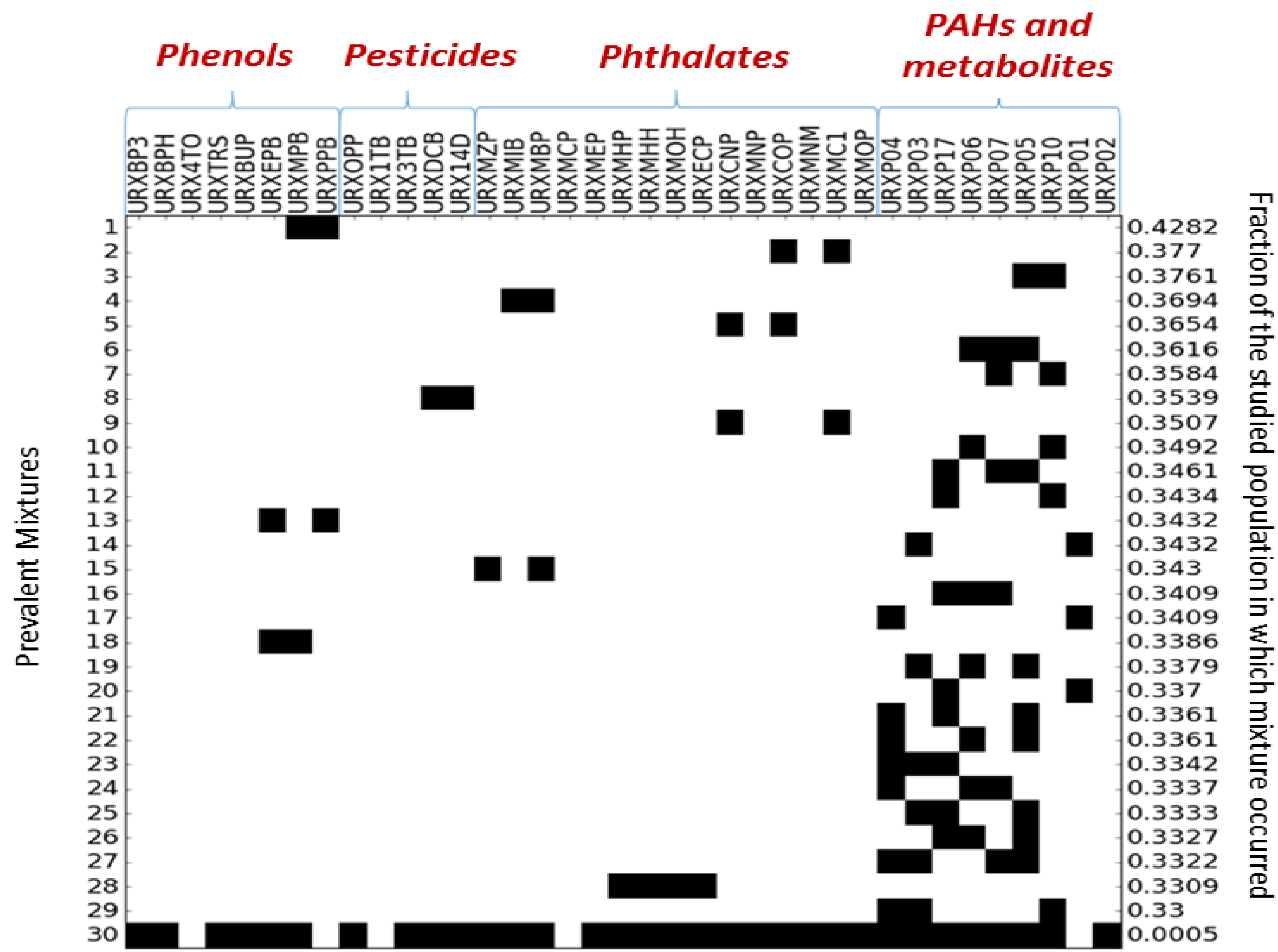
- Kapraun et al. (2017) used FIM to identify combinations of items (chemicals) that co-occur together within CDC NHANES samples from same individual

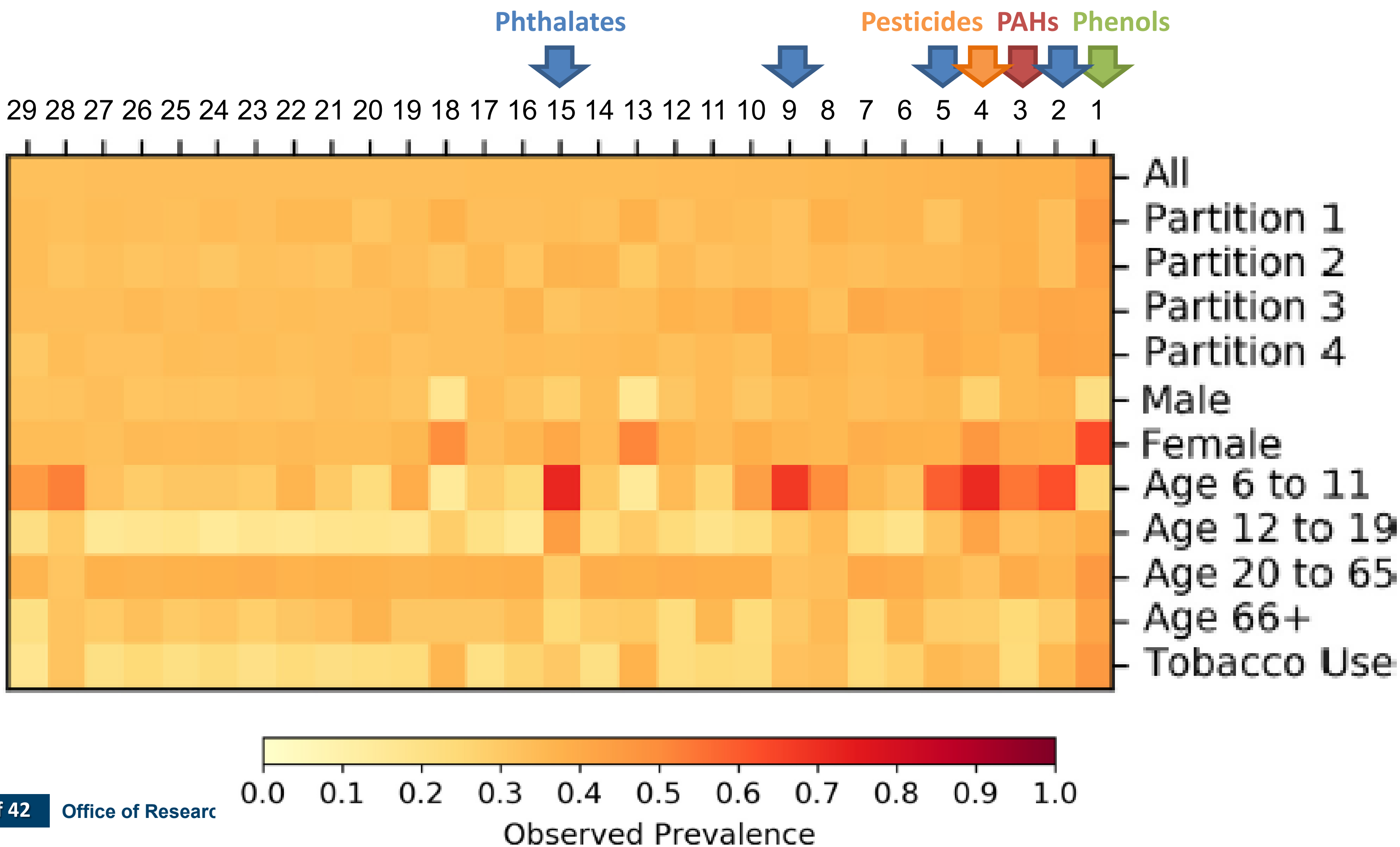
- Used total population median concentration as threshold for “presence”

- Identified a few dozen mixtures present in >30% of U.S. population



Kapraun et al. (2017)

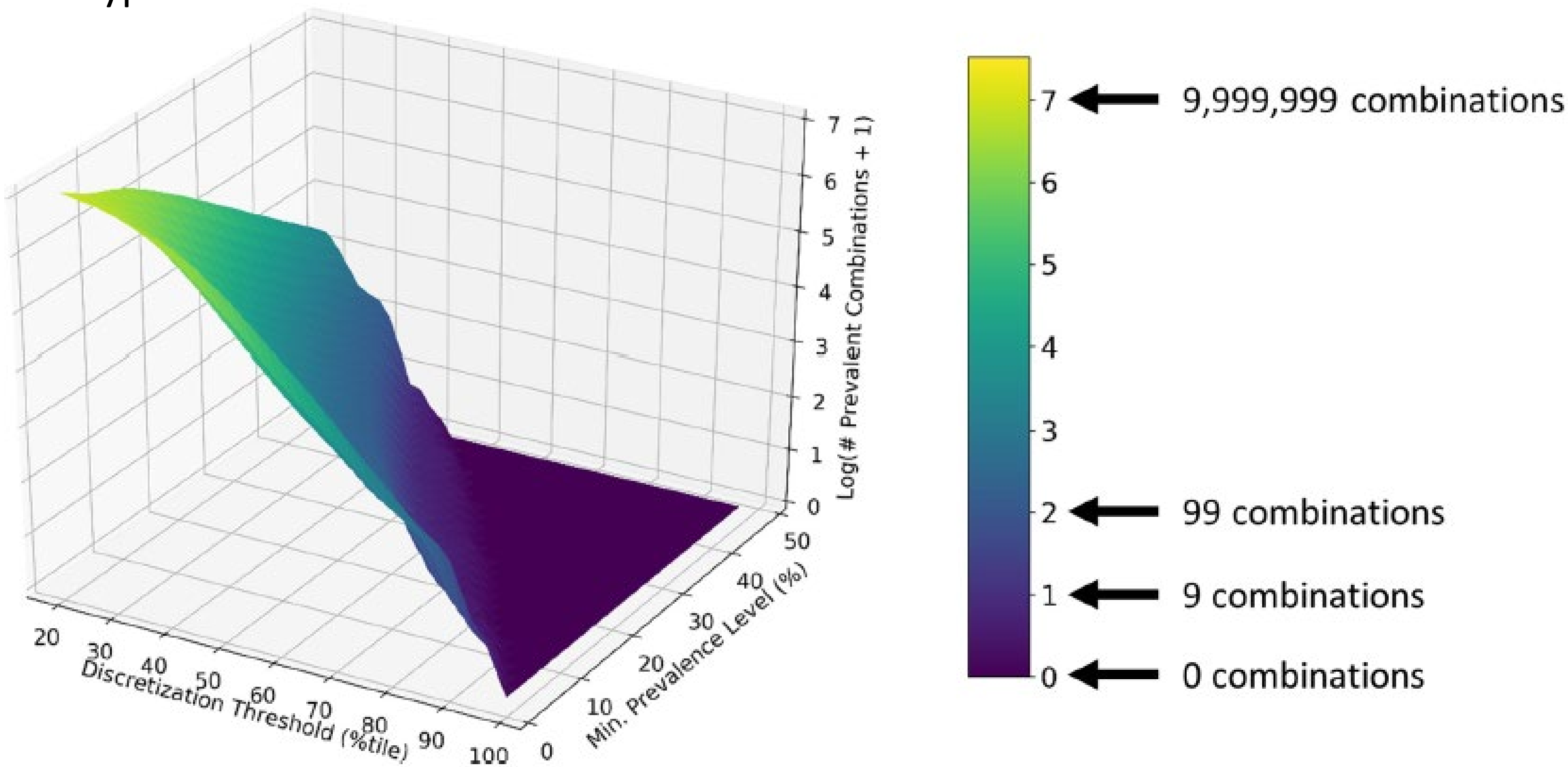
Demographic-Specific Prevalence of Combinations



Kapraun et al. (2017)

A Testable Number of Combinations

While high throughput screening (HTS) allows thousands of tests, there are millions of hypothetical combinations



“Exposure based priority setting” (NAS, 2017) allows identification of most important mixtures to test

Kapraun et al. (2017)

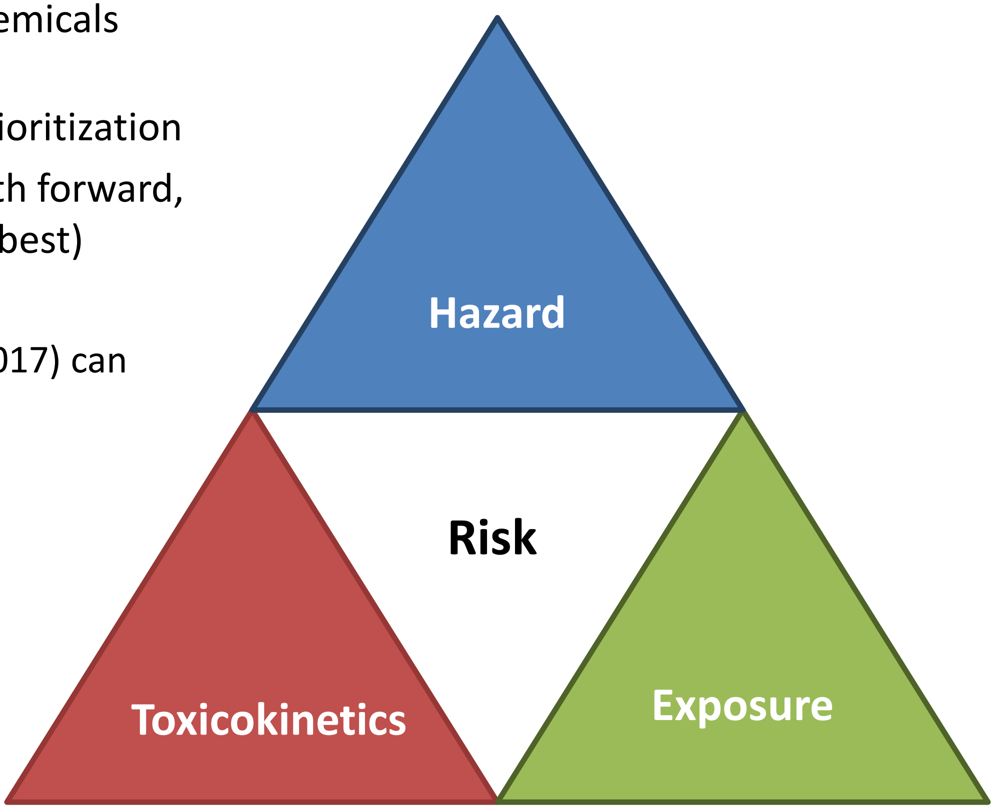
Conclusions

- We would like to know more about the risk posed by thousands of chemicals in the environment – which ones should we start with?

- Using *in vitro* methods originally developed for pharmaceuticals, we can make useful predictions of hazard and TK for large numbers of chemicals

- Exposure data is also key to risk-based prioritization
  - Consensus modeling provides one path forward, but only as good as available data (at best)

- EPA's CompTox dashboard (Williams et al, 2017) can help you:
  - Identify chemicals
  - Find toxicity data
  - Find lists of chemicals
  - Find metabolites
  - Identify products
  - Find toxicokinetic information
  - Get physicochemical properties
  - Batch download data



http://comptox.epa.gov/dashboard

The ExpoCast Project (Exposure Forecasting)

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References

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- Arnot, J. A.; Zhang, X.; Kircanski, I.; Hughes, L.; Armitage, J. Develop Sub-Module for Direct Human Exposures to Consumer Products. Technical Report for the U.S. Environmental Protection Agency; ARC Arnot Research & Consulting, Inc.: Toronto, ON, Canada, 2014.
- Bennett, D. H.; Furtaw, E. J., Fugacity-based indoor residential pesticide fate model. Environmental Science & Technology 2004, 38, (7), 2142-2152.
- Borgelt, C. (2012). Frequent item set mining. Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery, 2(6), 437-456.
- Breiman, L. (2001). Random forests. Machine learning, 45(1), 5-32.
- Breyer, Stephen. Breaking the vicious circle: Toward effective risk regulation. Harvard University Press, 2009
- Diamond JM. Assembly of species communities. Pp. 342–444 in Cody ML, Diamond JM (eds). Ecology and Evolution of Communities. Cambridge, MA: Belkap Press, 1975.
- Egeghy, P. P., et al. (2012). The exposure data landscape for manufactured chemicals. Science of the Total Environment, 414, 159-166.
- Ernstoff, A. S.; Fantke, P.; Huang, L.; Jolliet, O., High-throughput migration modelling for estimating exposure to chemicals in food packaging in screening and prioritization tools. Food and Chemical Toxicology 2017, 109, 428-438.
- Filer, Dayne L.. "The ToxCast analysis pipeline: An R package for processing and modeling chemical screening data." US Environmental Protection Agency: http://www. epa. gov/ncct/toxcast/files/MySQL% 20Database/Pipeline_Overview. pdf (2014)
- Goldsmith, M. R., et al. (2014). Development of a consumer product ingredient database for chemical exposure screening and prioritization. Food and chemical toxicology, 65, 269-279.
- Huang, L.; Ernstoff, A.; Fantke, P.; Csiszar, S. A.; Jolliet, O., A review of models for near-field exposure pathways of chemicals in consumer products. Science of The Total Environment 2017, 574, 1182-1208.
- Huang, L.; Jolliet, O., A parsimonious model for the release of volatile organic compounds (VOCs) encapsulated in products. Atmospheric Environment 2016, 127, 223-235.
- Jolliet, O.; Ernstoff, A. S.; Csiszar, S. A.; Fantke, P., Defining Product Intake Fraction to Quantify and Compare Exposure to Consumer Products. Environmental Science & Technology 2015, 49, (15), 8924-8931.
- Judson, R. S., Magpantay, F. M., Chickarmane, V., Haskell, C., Tania, N., Taylor, J., ... & Houck, K. A. (2015). Integrated model of chemical perturbations of a biological pathway using 18 in vitro high-throughput screening assays for the estrogen receptor. Toxicological Sciences, 148(1), 137-154.
- Kaewkhaw, R., et al. (2016). Treatment paradigms for retinal and macular diseases using 3-D retina cultures derived from human reporter pluripotent stem cell linestreatment design using PSC-Derived 3-D retina cultures. Investigative ophthalmology & visual science, 57(5), ORSFl1-ORSFl11.
- Kapraun, Dustin et al., "A Method for Identifying Prevalent Chemical Combinations in the US Population," Environmental Health Perspectives, 2017
- Kavlock, Robert, et al. "Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management." Chemical research in toxicology 25.7 (2012): 1287-1302.
- MacLeod, Matthew, et al. "The state of multimedia mass-balance modeling in environmental science and decision-making." (2010): 8360-8364
- National Academies of Sciences, Engineering, and Medicine. (2017). Using 21st century science to improve risk-related evaluations. National Academies Press.
- National Research Council. (1983). Risk Assessment in the Federal Government: Managing the Process Working Papers. National Academies Press.
- National Research Council. (2007) Toxicity testing in the 21st century: a vision and a strategy. National Academies Press.
- O'Connell, S. G., Kincl, L. D., & Anderson, K. A. (2014). Silicone wristbands as personal passive samplers. Environmental science & technology, 48(6), 3327-3335.
- Park, Youngja, H., et al. "High-performance metabolic profiling of plasma from seven mammalian species for simultaneous environmental chemical surveillance and bioeffect monitoring." Toxicology 295:47-55 (2012)
- Pearce, Robert, et al. "httk: R Package for High-Throughput Toxicokinetics." Journal of Statistical Software, 2017
- Phillips, Katherine A., et al. "High-throughput screening of chemicals as functional substitutes using structure-based classification models." Green Chemistry (2017).
- Phillips, Katherine A., et al. "Suspect Screening Analysis of Chemicals in Consumer Products", accepted at Environmental Science & Technology.
- Rotroff, Daniel, et al., (2010) "Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening." Tox. Sciences 117(2), 348-58
- Schmidt, Charles W. "TOX 21: new dimensions of toxicity testing." Environmental health perspectives 117.8 (2009): A348.
- Shin, H.-M.; McKone, T. E.; Bennett, D. H., Intake Fraction for the Indoor Environment: A Tool for Prioritizing Indoor Chemical Sources. Environmental Science & Technology 2012, 46, (18), 10063-10072.
- Shin, Hyeong-Moo, et al. "Risk-based high-throughput chemical screening and prioritization using exposure models and in vitro bioactivity assays." Environmental science & technology 49.11 (2015): 6760-6771.
- Wallace et al., "The TEAM Study: Personal exposures to toxic substances in air, drinking water, and breath of 400 residents of New Jersey, North Carolina, and North Dakota ." Environmental Research 43: 209-307 (1987)
- Tornero-Velez et al. (2012) "Biogeographical Analysis of Chemical Co-Occurrence to Identify Priorities for Mixtures Research": Risk Analysis, 32(2) 224-236
- Wambaugh, John F., et al. "High-throughput models for exposure-based chemical prioritization in the ExpoCast project." Environmental science & technology 47.15 (2013): 8479-848.
- Wambaugh, John F., et al. "High Throughput Heuristics for Prioritizing Human Exposure to Environmental Chemicals." Environmental science & technology (2014).
- Wambaugh, John F., et al. "Evaluating In Vitro-In Vivo Extrapolation" accepted at Toxicological Sciences,.
- Wang, Y.-H. (2010). "Confidence Assessment of the Simcyp Time-Based Approach and a Static Mathematical Model in Predicting Clinical Drug-Drug Interactions for Mechanism-Based CYP3A Inhibitors." Drug Metabolism and Disposition 38(7), 1094-1104
- Wetmore, Barbara A., et al. "Integration of dosimetry, exposure and high-throughput screening data in chemical toxicity assessment." Toxicological Sciences (2012): kfr254.
- Wetmore, Barbara A., et al. "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing." Toxicological Sciences 148.1 (2015): 121-136.
- Zhang, X.; Arnot, J. A.; Wania, F., Model for screening-level assessment of near-field human exposure to neutral organic chemicals released indoors. Environmental science & technology 2014, 48, (20), 12312-12319.