**Theme V – Systems Biology and Big Data**

**Coordinators**

Catherine Mahony, Procter & Gamble, Bagshot, Surrey, United Kingdom  
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**Oral Presentations**

**Session V-1: Harnessing Big Data for Decision Making at Different Levels**

**Co-Chairs**

Thomas Knudsen, US EPA, Research Triangle Park, NC, United States  
Gladys Ouédraogo, L’Oréal R&I, Aulnay sous Bois, France

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**V-1-342**

**Use of transcriptional profiling in *in vitro* systems to determine the biological activity of chemicals of interest**

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The development of *in vitro* assays to assess chemical safety, as alternatives to animal testing, has become an important undertaking in toxicology research. Moreover, the research in this field has been moving more into the definition of chemical’s mechanism of action, with clear identification of key events leading to adverse health effects. The ultimate goal is to rely less on apical endpoints, derived from *in vivo* studies, for the assessment of chemicals’ safety. Thus, the need is not only for *in vitro* predictive toxicological assays, but also for these assays to provide relevant information of the biological activity associated with chemicals of interest, and with that, a better understanding of the underlying mechanisms of potential toxicity. We have focused our research in the use of transcriptional profiling in *in vitro* systems, a small number of cultured cell types enriched in relevant pathways for various modes of action, to determine the biological activity of chemicals of interest. Our data supports the hypothesis that transcriptional profiling of chemical-treated cultured cells, in a time and dose-dependent manner, provides data to characterize chemicals of interest based on their biological activity. This information can lead to a better understanding of key events underlying mechanisms of potential toxicity.

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**V-1-659**

**A model for estimating systemic toxicity points-of-departure using chemical, biological, kinetic and study covariates**

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Since 2013, repeated-dose systemic toxicity for cosmetics can no longer be assessed utilizing animal testing. This project aims to advance predictive approaches in this field by leveraging different data types – cheminformatics, bioactivity, kinetic parameters, legacy study covariates – to predict systemic toxicity points-of-departure (POD). A cross-validated and externally-tested random forest model was built using 1201 chemicals to derive estimates of study-level POD. Baseline performance was set with the study covariates alone – ~20% of the POD variance, while adding the mean POD for each chemical explained ~70% of the variance; giving a performance benchmark. The model built using all features explained 38% of the variance in the external test set compared to 20-30% with isolated features. The model output provides a reliable estimate of POD with uncertainty quantified. This can be used with other data in a weight of evidence approach when evaluating repeated dose systemic toxicity.
Human brain model for analysis of pathways (Brain MAPS)

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Brain MAPs is envisioned as a novel high throughput screening platform to recapitulate critical aspects of human central nervous system (CNS) development in vitro for neurotoxicological studies. Specifically, it is designed to recapitulate the cell phenotype diversity and tissue cytoarchitecture characteristic of the developing human CNS while maintaining the requisite sensitivity to detect cell phenotype-specific toxicity and identify the correlated signaling pathways disrupted by drug/chemical exposure. This is achieved using engineered, chemically-defined culture systems, diverse high-throughput measurements including imaging and omics profiling, and modeling these data to reproducibly instruct in vitro morphogenesis of CNS tissues from human neural stem cells (hNSCs). The hNSCs have been patterned to direct biomimetic tissue growth and differentiated to cell types found throughout the human embryo’s rostrocaudal and dorsoventral neuraxis. Thus, Brain MAPs enables development of a pipeline for phenotype-specific, quantitative high-throughput developmental neurotoxicity studies.

Mechanistic modeling of developmental defects through computational embryology

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An important consideration for the 3Rs is to identify developmental hazards of drugs and environmental chemicals utilizing mechanism-based in vitro assays (e.g., ToxCast) and in silico predictive models. Steady progress has been made with multicellular agent-based models (ABMs) that recapitulate morphogenetic drivers for angiogenesis, somitogenesis, urethrogenesis, and palatogenesis. Next up are ABMs for the neurovascular unit, endocardial cushions, and neural tube closure. These models offer a heuristic approach to reconstruct tissue dynamics from the bottom-up, cell-by-cell and interaction-by-interaction. Individually, they simulate emergent phenotypes and can be used to predict adverse outcomes or “cybermorphs” that bring an AOP to life through multicellular computational and spatial dynamics. Collectively, their compilation into an integrated “virtual embryo” motivates the construction of novel ontology systems that integrate molecular pathways, cellular behaviors, and in vitro data on chemical-biological interactions with extant knowledge of embryology.

This abstract does not reflect US EPA policy.
Session V-2: Future of Big Data in 3Rs and Recommendations – Round Table

Chair
Catherine Mahoney, Procter & Gamble, Bagshot, Surrey, United Kingdom

V-2-494

Future of big data in 3Rs and recommendations

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This roundtable session will explore what big data means for the 3Rs and how a deeper understanding of biology might play a role in eventually redefining decision making. Panellists will review the progress being made in big data for the 3Rs, attempt to lay out key challenges and engage in discussion on what is needed to further its practical application, both now and in the future. To harness big data and create meaning from it the infrastructure and resources for storage and analysis need to be up to par, we need to be able to extract relevant data and mine it for research purposes and as with any other research effort having a clear hypothesis, showing methodology and describing confidence in results is paramount.
Session V-3: Best Practices for Modeling Data

Co-Chairs
Raymond R. Tice, National Institute of Environmental Health Sciences, Durham, NC, United States
Glenn Myatt, Leadscope Inc., Columbus, OH, United States

V-3.710
Developing systems models for safety decision making: Challenges for improving confidence
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Growth in the available data within the biological and toxicological community is increasing the range of tools available to integrate this information to aid chemical risk assessment in the development of non-animal approaches. However, transforming available data sets and tools for risk assessment highlights challenges around transparency, applicability, knowledge and estimation of uncertainty. Together these emphasise the need for best practice, analogous to those already undertaken in other fields, to increase confidence in the application and ultimately the regulatory submission of mathematical and computational models.

We provide examples in the development of statistical, mechanistic and quantitative systems models on how the approximation of the underlying biological system could be defined as fit for purpose. We further show how these disparate sources of information can inform on emergent properties to rationalise dose metrics such as tipping points between adaptive and adverse effects useful to risk assessment decision.

V-3.647
The development of in silico toxicity protocols
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This project is generating a series of protocols to support the prediction of a series of major toxicological endpoints (e.g., genetic toxicity, carcinogenicity, acute toxicity, reproductive and development toxicity). These protocols are being developed through an international cross-industry consortium to reflect the state-of-the-art in computational toxicology for hazard identification and characterization. The consortium is led by Leadscope and includes 45 organizations from international regulatory agencies and government research laboratories in the US, Canada, Japan, and Europe as well as large companies from the various industrial sectors (e.g., pharmaceutical, food, cosmetics, agrochemicals), academic groups and other stakeholders.

The protocols will ensure any in silico toxicological assessments are performed in a consistent, repeatable, well-documented and defensible manner. This includes how to assess the reliability and relevance of data/predictions, how an expert review of the results may be performed and how an overall assessment may be performed based on the weight-of-the-evidence.

V-3.694
Open analytical challenges to crowdsourcing biomedical research
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Explosive growth in high-dimensional biomedical data generation has led to the need for rapid development and benchmarking of advanced computational methods to produce actionable knowledge from these datasets. A popular approach to benchmark such methods and understand the capacity for scientific insight from a dataset is the organization of unbiased crowdsourcing-based science competitions/challenges. DREAM engages diverse communities of computational experts to leverage the “wisdom of crowds” to solve specific biomedical problems. DREAM organizers have launched over 35 successful challenges addressing pressing computational issues and biomedical problems. DREAM challenges, and related efforts, provide a promising opportunity to effectively assimilate the rich knowledge embedded within the research community and establish community consensus in research outcomes.
Session V-4: Resources and Tools for State of the Art Systems Modeling

Co-Chairs
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Hiroaki Kitano, Systems Biology Institute, Tokyo, Japan

V-4-525

**In vitro-based high-throughput/high-content screening and omics-driven informatics support integration of systems biology and big data in alternative testing methods**

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The rapidly developing “Big Data era” in toxicology involves generation of large amounts of safety testing data and the need to interpret the results relative steadily increasing amounts of related information in databases. Cell culture models serve for high-throughput screening analysis, allowing libraries of drugs, chemicals and nanomaterials to be effectively assessed and ranked for cytotoxicological properties. In parallel, microscopy-driven high-content analyses of morphology and immunochemical markers, and genomic profiling data opens for mechanistic cytopathological interpretation. Bioinformatics tools additionally permit overview and visualization of new results relative existing relevant data. Ideally, the combined use of the above technologies allows for coupling to adverse outcome pathway descriptions. Tiered workflows combine these methods into safety evaluations building on systems toxicology. Applications and challenges related to the above concepts will be discussed.

References

V-4-207

**A new tool for aligning assay endpoints to adverse outcome pathways**

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A critical toxicological challenge is linking endpoints measured in non-animal approaches to adverse physiological responses in vivo. The adverse outcome pathway (AOP) framework allows placement of these molecular, cellular, and tissue-level endpoints into a biologically relevant context. The National Toxicology Program’s Integrated Chemical Environment (ICE) web resource houses curated data from in vivo, in vitro, and in silico endpoints. We present a new feature of ICE that maps assay endpoints to key events within AOPs. We demonstrate how this feature can be used to identify data gaps, build confidence in mechanistic plausibility and relevance, and provide insights on potential adverse outcomes using AOPXplorer. This presentation will use the skin sensitization AOP and putative AOPs for androgen and estrogen receptor pathways to demonstrate the utility of this feature.

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Development of a repeated dose toxicity mode of action-based ontology

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Recent research programmes in toxicology and risk assessment showed the critical importance of understanding modes of action of chemicals to enable predictions of human health effects. High-throughput technology generates a considerable amount of data. It triggers the need for a structured system, an ontology, to support toxicity predictions. Developing a repeated dose toxicity ontology (RDTO) requires addressing four main pillars: chemistry; kinetics & exposure; mode of action and toxicological effects. By integrating multiple adverse outcome pathways (AOPs) and their links, the RDTO produces an AOP-network. It reflects a realistic in vivo-like toxicological exposure-response scenario, captures homeostatic adaptations of biological systems, defines critical key events (KEs) and quantify relevant key event relationships (KERs). The RDTO waives in vivo testing while enabling human-based in vitro experimentation, and supports the use of AOPs in contemporary risk assessment.

Computational modeling: Moving from data mining to understanding systems

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Increased computational processing speeds and the availability of seemingly limitless data storage have brought about the age of “big data” and “deep learning” which have become almost synonymous with “computational approaches”. However, rather than replace animal research these trends have often led to worsening scientific, clinical and ethical outcomes. Lost in all this, is the power of certain forms of theoretical computational modeling. These alternate methods allow for rapid investigation using abstractions and evolution. Here we present a study of neurodegeneration using spatial neural networks that may have broad applicability to aging and age-related conditions such as dementia. We demonstrate how these simulations may help explain behaviors seen in systems ranging from stem cell cultures to human neural activity. In doing so, we underscore the power of such approaches to go beyond brute force data mining and help researchers gain deeper understanding without the use of animals.