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Editorial

AI and the Toxicology Wilderness

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For traditional and practical reasons, we regard pharmacology and toxicology as sister disciplines, placing them together in print, as they are on this journal. Indeed, the two fields are complementary, but, like any pair of sisters, they are far from equivalent. While pharmacology poses many research challenges that are far from trivial, most people regard toxicology as far messier.

The basis for this distinction is obvious. Pharmacology is focused primarily on the goal of, and implications of, medicating one specific physiological target or pathway. Toxicology, by contrast, is the sum of any adverse direct effects of this targeting, plus all other unintended consequences impinging on any other pathway or target in the body.

Simply put, toxicology tries to account for everything we don't want, and most of what we never anticipated. This is not easy. For decades, the FDA has brow-beat us with the goal of producing drugs that are as safe as they are effective, yet most of us are still like children hearing nursery rhymes that teach about actions and consequences. We know we should avoid things that hurt us, but we're still not great at guessing what will cause harm, and why.

Fortunately, between a wealth of case studies, empirical observations, and rigorous Phase II, III and IV clinical trial data, as well as tremendous post-genomic advances in molecular physiological understanding, we really ought, now, to have the basis for strong predictive toxicology. Surely, our Phase II and III clinical success rates ought to be shooting up, even for relatively novel chemical entities. Surely the number of tox-related suspensions of approved drugs ought to plunge.

Of course, we all know that the phrase 'ought to' does not equate to 'will', and many of us appreciate that a key reason for the shortcoming is one of analytical complexity - the volume of available toxicological and physiological data is too large and complicated to humanly process and, until very recently, has even relegated most artificial intelligence (AI) methods to modest incremental goals of rationalizing effects within a narrow subset of human physiology, for mere subclasses of patients. Ultimately, our capacity for generally predictive toxicology has been hindered by the many competing intoxication mechanisms, and by tremendous variation in physiological response and susceptibility even within a fairly tight patient cohort.

That now, finally, seems destined to change, thanks to new algorithms.

The year 2017 should go down in history as an amazing pivot point in AI. Forget procedurally simple games like Chess and Go; last year AI algorithms beat top professional Poker players at No-Limit Texas Hold'Em - a battle more akin to psychological warfare than statistical assessment. AI produced an app that can learn computer programming; set loose with a compiler and some technical specifications, the app managed to develop a visual recognition algorithm whose accuracy exceeded that achieved by human programmers. One of the most wild and unsettling achievements is the documented behavior of adaptive experimental chatbots produced by Facebook which, when set loose to chat among themselves, began their conversation in English but unexpectedly learned to develop their own increasingly impenetrable dialect.

Perhaps these remarkable achievements in adaptive learning do not seem obviously salient to challenges in toxicology but they actually do illustrate precisely the sort of cognitive flexibility that may best uncover novel data motifs underlying tox trends manifest in drug design and utilization. Specifically, the data landscape is so complex that perhaps it's best to remove human biases entirely. While conventional started with humanly preconceived instructions for where and how to search, now algorithms can shed that entirely. Imagine a master process instructed only with the most bare-bones questions (e.g. "Will compound X kill me?"or, "Is Y likely to be carcinogenic?"), given lattitude to search simultaneously for answers and for the best algorithms and search parameters by which to pursue these queries. What will that process learn toxicology principles that we might never have dreamed of?

State-of-the-art AI methods are evolving as rapidly for toxicology as for any data-driven discipline, and this year's tools may be next year's foils, but let's highlight two algorithm classes that demonstrate major initial promise in enabling adaptive, predictive tox assessments:

- Systems Toxicology, whereby variations within extensive bodies of molecular profiling data are assessed against toxicity trends, producing systems of differential equations that foster inference of the causal networks underlying observed toxic effects, and
- Deep Learning, which applies sophisticated neural network techniques (algorithmically far superior to the ancient chemometric principles that we abandoned a generation ago) to systematically remap problems into different conceptual layers, en route to powerfully predictive associations that explain chemically adverse outcomes.

Given the highly fluid nature of these emerging disciplines, it is difficult to recommend the best resources to adopt for AI-driven toxicological assessments, but it is worth mentioning that a demonstrably successful deep learning toolkit (including subroutines, sample data and documentation) has been bundled together as DeepTox (http://bioinf.jku.at/research/DeepTox/tox21.html). Good candidates for a comparable, publically available systems toxicology suite are more elusive, however one place to watching for developments is the sbv IMPROVER systems toxicology challenge (https://www.sbvimprover.com/challenge-4).

Today, we're still in the wilderness, but there is finally a light. Perhaps that light is AI, leading us toward toxicology deliverance.

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