New Approach Methodologies (NAMs) to advance points of departure (PoDs) estimation

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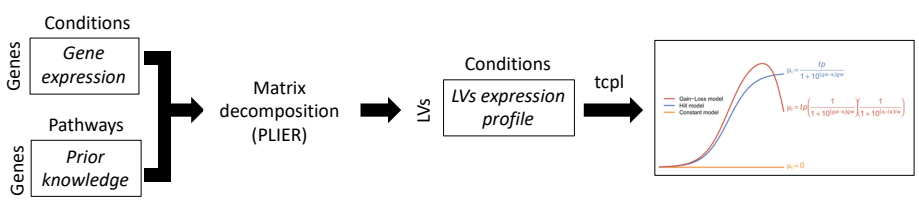
1 INTRODUCTION

In a next-generation risk assessment (NGRA), human health safety decisions are based in large part on the margin of safety, which is the ratio between the maximum plasma concentration for a given chemical exposure scenario and the point of departure (PoD), the concentration at which the chemical induces bioactivity in relevant *in vitro* assays[1]. When using high throughput transcriptomics data, current approaches for PoD estimation mostly rely on single key gene targets, however, since genes do not work alone but within complex molecular networks, they lack the diagnostic capability to provide a comprehensive view of biological activity. Here we set to address this issue by exploring a gene co-expression approach that summarize gene expression profiles into pathway activity in a both data and biology driven way and by then modelling pathway-level bioactivity.

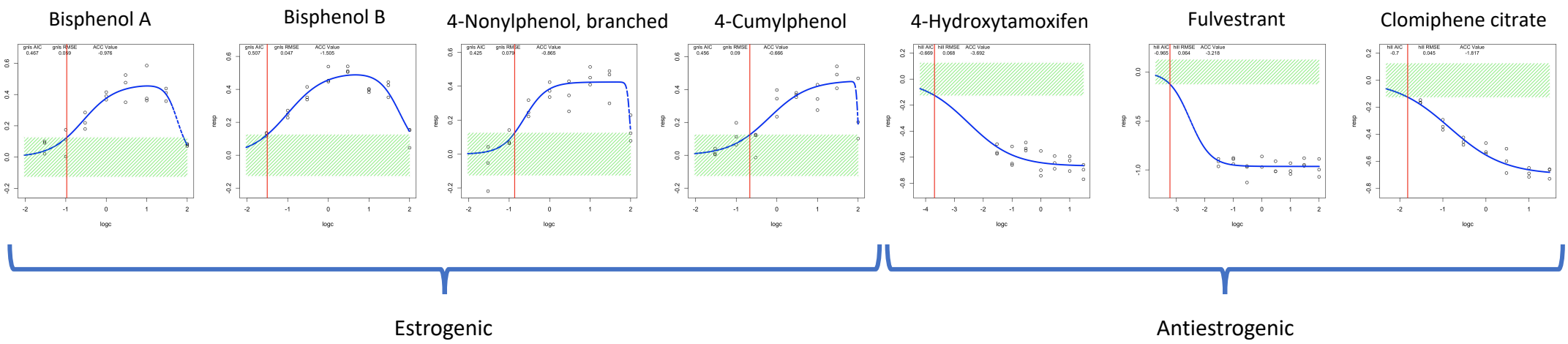
2 MATERIALS & METHODS

We developed a computational workflow leveraging a matrix factorization approach (PLIER)[2] whose decomposition of gene expression into latent variables (LVs) is driven by prior knowledge. LVs activity was evaluated using the toxcast pipeline (tcpl)[3]. We validated the workflow on a public dataset of MCF7 concentration-response data for 44 compounds with different mode of action (MoA)[4]. We then translated its application to an in-house dataset obtained by screening HepG2 cells across 7 concentrations of relevant chemicals for 24 hrs. The dataset included compounds with very low level of bioactivity (coumarin, caffeine, phenoxyethanol and niacinamide)[5] and compounds for which an exposure scenario was not currently available (andrographolide, flutamide and triclosan).



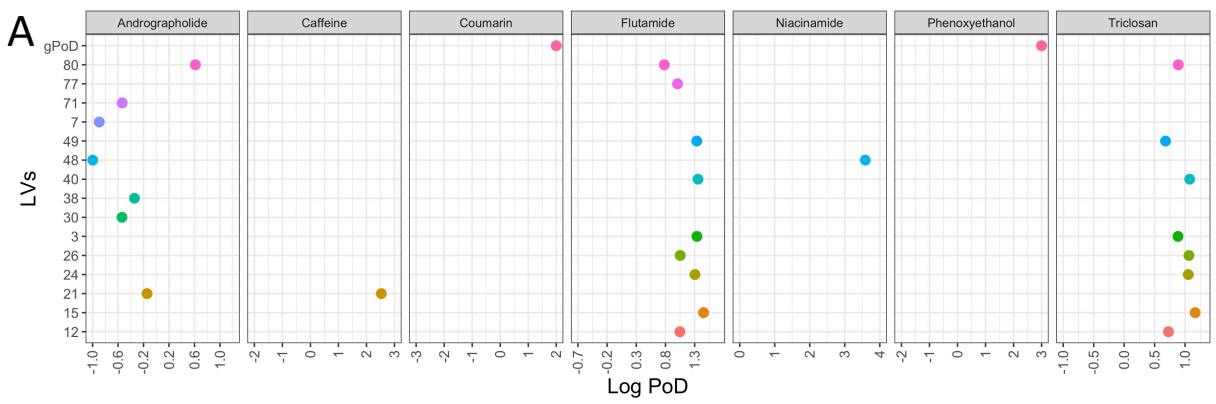
3 RESULTS

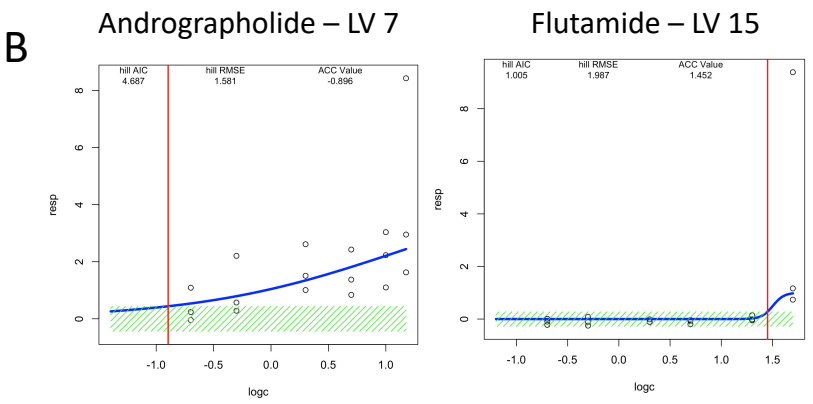
Application of the computational workflow to the MCF7 dataset confirmed its ability to identify known MoA. Estrogenic and antiestrogenic compounds were found to share activity for the an LV associated with estrogen receptor related functions. The activity profile of this LV was found to have similar potency (similar estimated PoDs) among compounds belonging to the same class. In addition, response for the agonists was found to be positive and negative for the antagonists.



When translating the approach to an in-house dataset, we could not detect much activity for low bioactive compounds but relevant activity was found for those lacking of an exposure scenario (fig. A).

For some of the compounds we identified activity for LVs associated with stress response. As an example, andrographolide and flutamide were found to elicit oxidative and endoplasmic reticulum (ER) stress, respectively, with different potencies (fig. B).





4 DISCUSSION

These results demonstrate the effectiveness of using PLIER for concentration-response analysis and its strength of providing information of activity on a pathway level, represent a promising tool to support the development of a framework with the ability to estimate more reliable PoDs with the long-term goal of improving current risk assessment strategies for chemicals using NAMs.

REFERENCES

[1] Baltazar et al. A Next-Generation Risk Assessment Case Study for Coumarin in Cosmetic Products. 2021. *Toxicological Sciences*
[2] Mao et al. Pathway-level information extractor (PLIER) for gene expression data. 2017. *Nature methods*
[3] Filer et al. tcpl: the ToxCast pipeline for high-throughput screening data. 2017. *Bioinformatics*
[4] Harrill et al. High-Throughput Transcriptomics Platform for Screening Environmental Chemicals. 2021. *Toxicological Sciences*
[5] Hatherell et al. Identifying and Characterizing Stress Pathways of Concern for Consumer Safety in Next-Generation Risk Assessment. 2020. *Toxicological Sciences*