Deciphering the quantitative relationship between chemical kinetics and Nrf2 pathway dynamics

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Introduction

Oxidative stress resulting from exposure to certain xenobiotics plays an essential role in the development of drug-induced liver injury (DILI). Nrf2 (Nuclear factor erythroid 2-related factor 2) is an important regulator of the oxidative stress response (OSR) as it regulates various target genes that help to maintain cellular homeostasis, such as Srxn1 (Sulfiredoxin-1). It is not yet well understood what is the quantitative link between chemical kinetics, Nrf2 activation dynamics and that of Nrf2 downstream targets. Here, we developed a quantitative dynamic model based on detailed time course measurements with HepG2 reporter cell lines. Our model integrates in vitro chemical kinetics data with dynamics data of Nrf2 and Srxn1, following single exposure to individual chemicals i.e., Sulforaphane (Sul) and CDDO-me (CDDO) and repeated exposure to various concentrations of these chemicals.

Modeling Strategy

We adapted the virtual cell based assay model[1] to describe the in-vitro chemical kinetics of Sul and CDDO. We used ordinary differential equations to describe Nrf2 signaling (Fig. 1A-B). Nrf2-induced Srxn1 was described using a multiplicative mechanism, i.e. the presence of both unmodified and modified Nrf2 induced Srxn1 expression. We used non-linear mixed-effect modeling with partially hierarchical parameters to calibrate model parameters to the data with a Bayesian approach (Fig. 1C).

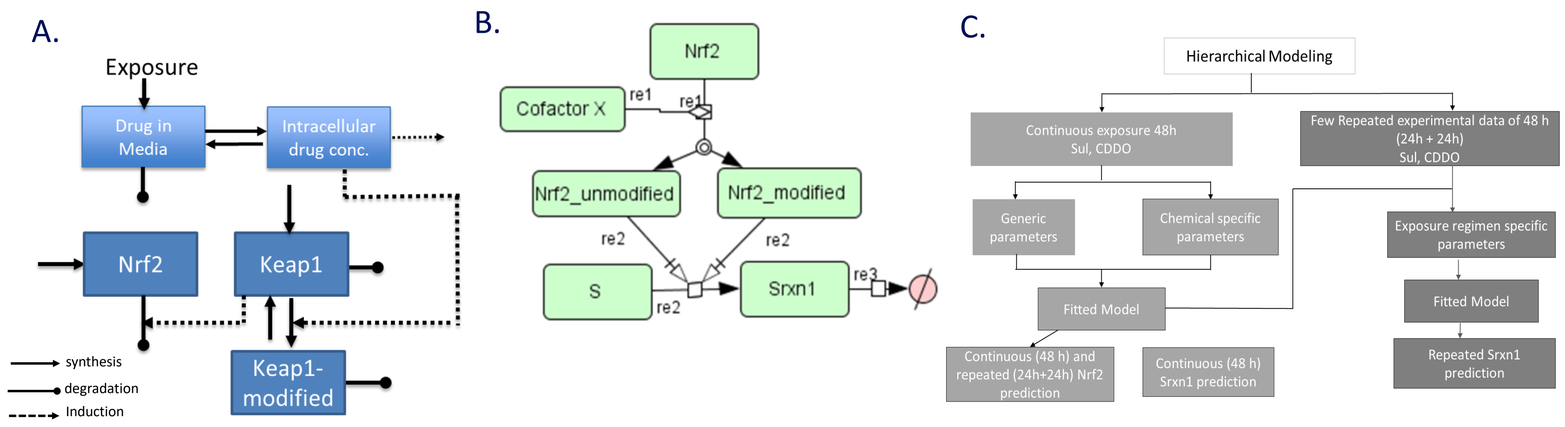

Fig 1: Modeling strategy to describe chemical kinetics and Nrf2 dynamics (A), and Srxn1 dynamics (B). C) Fitting strategy with non-linear mixed-effects modelling.

Abbr. Nrf2 – (Nuclear factor erythroid 2-related factor 2) ,Srxn1- (Sulfiredoxin-1), Keap1- (Kelch-like ECH-associated protein 1), S-(Substrate) , CofactorX –(a hypothetical set of Nrf2 modifiers)

Modeling results

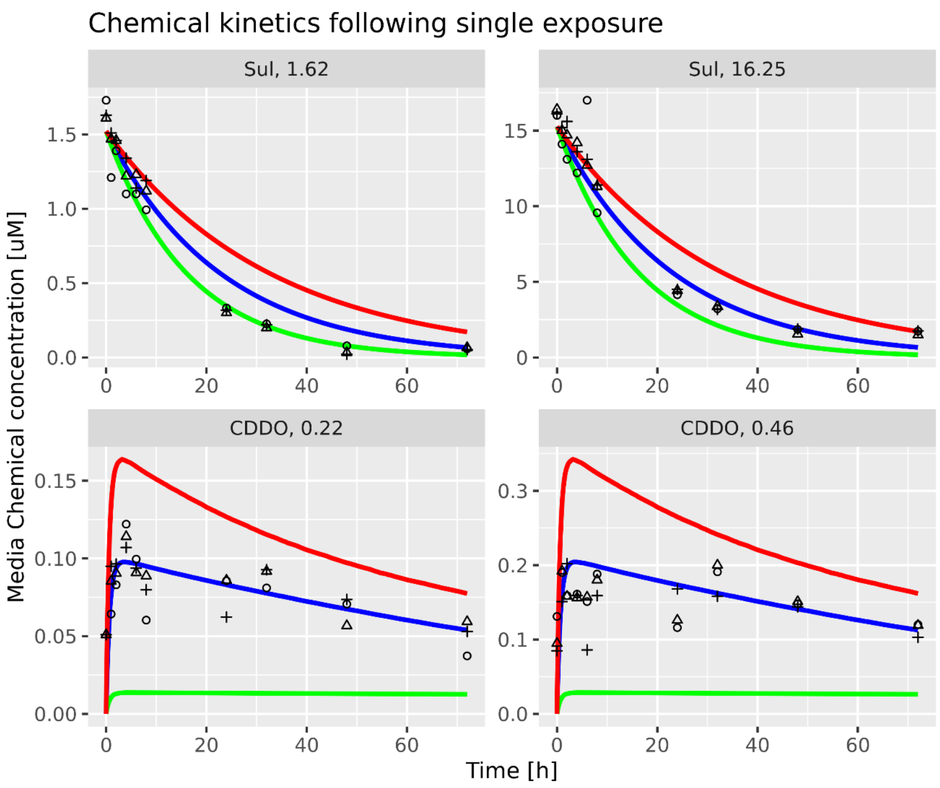

Fig. 2: Simulations and data of in vitro concentrations over time.

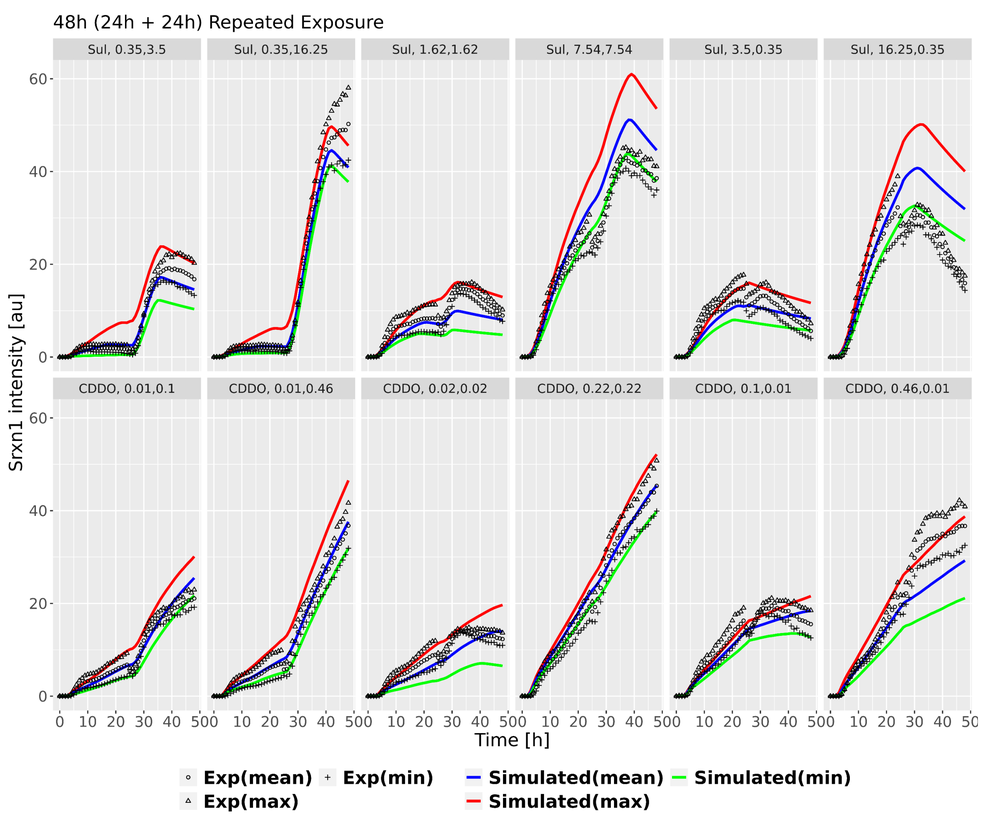

Fig. 3: Simulations and data of Srxn1 levels in HepG2 cells in vitro.

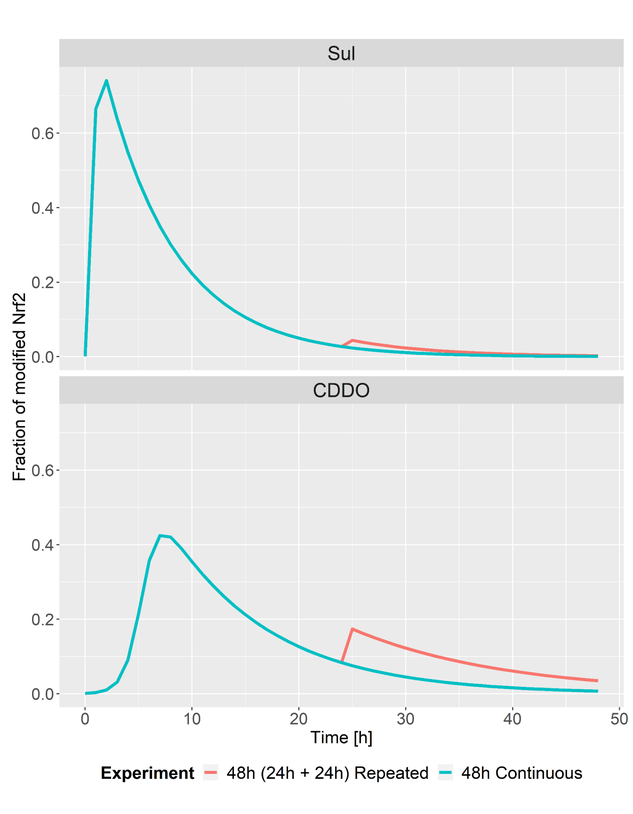

Fig. 4: Model-predicted fraction of modified Nrf2 over time.

Conclusions and Perspectives

- Our model mechanistically describes the relationship between chemical kinetics and Nrf2 pathway dynamics under various exposure conditions.
- CDDO has a long half-life resulting in sustained Nrf2 activation, whereas Sul degrades quickly resulting in a sharp rise and decay of Nrf2.
- Srxn1 expression requires time-, compound-, and exposure regimen specific modulation of Nrf2 activity.
- A full understanding of Nrf2-mediated Antioxidant Response Element (ARE) genes activation requires detailed dynamic information on Nrf2 binding partners and co-factors.
- Our model can in the future be used together with PBPK-based tissue dosimetry in-vitro in-vivo extrapolation (IVIVE) for repeat dose adaptive and adverse stress response effects as part of a human focused risk assessment.

References

Paini et al. From in vitro to in vivo : Integration of the virtual cell based assay with physiologically based kinetic modelling, Toxicology in Vitro 45 (2017).