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Systems modelling of quantitative adverse outcome pathways:

progress on the temporal integration of toxicokinetics and beyond

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ecetoc

Workshop on Time4NGRA

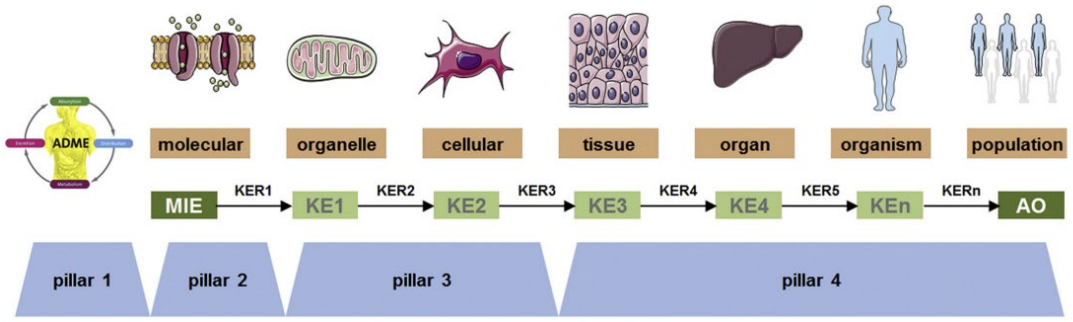
Brussels & online, 2023-11-7&8

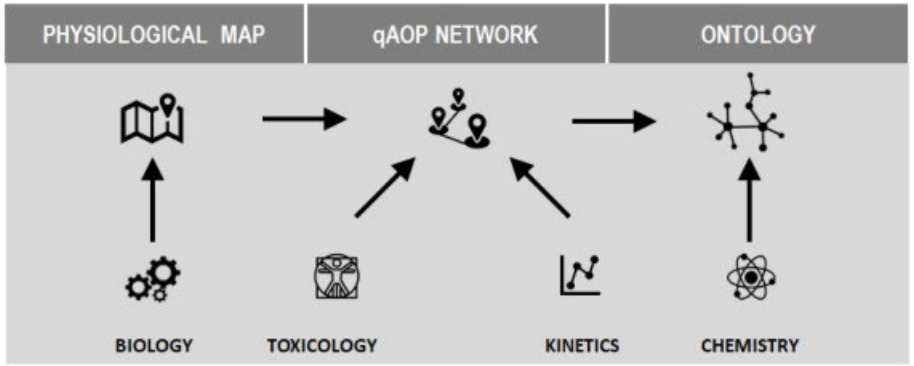
Outline

- Background
- Systems modelling of quantitative AOP (qAOP) and its integration with PK
- Temporal consideration and dose/response-response relationship in RA and NGRA
- Example in visualization and computational analysis
- Conclusions and perspective

Background information

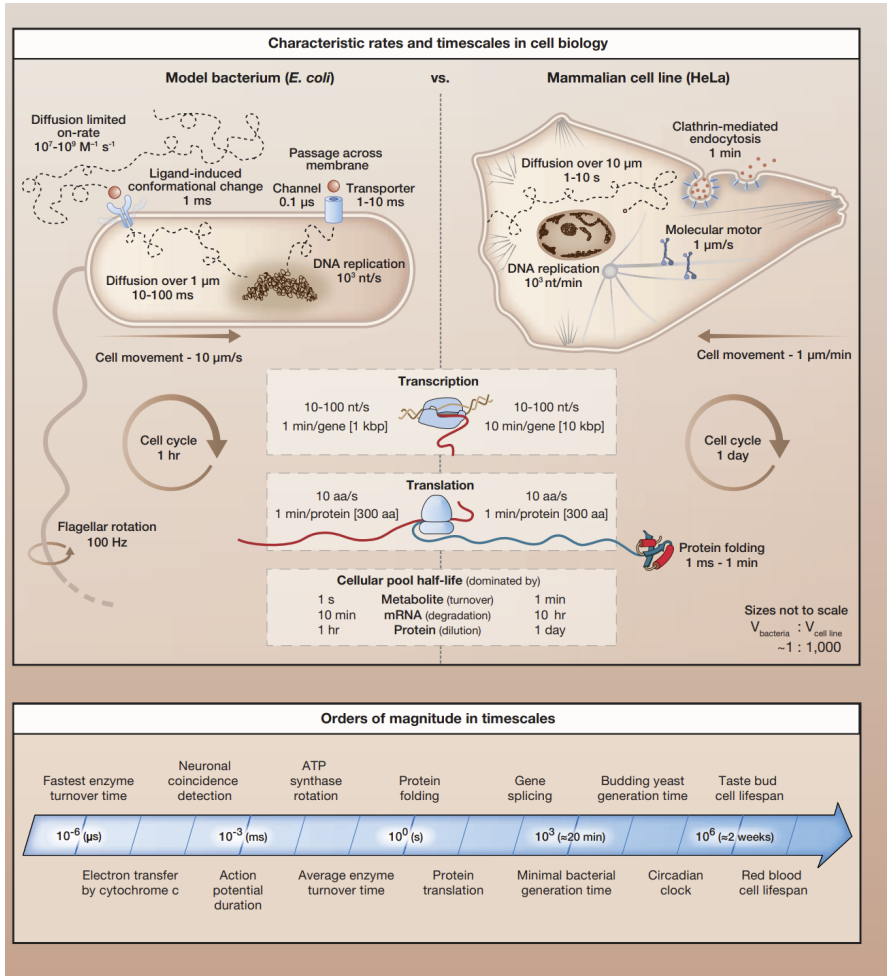
Adverse outcome pathway (AOP) and integration with (pharmaco/toxico)kinetics



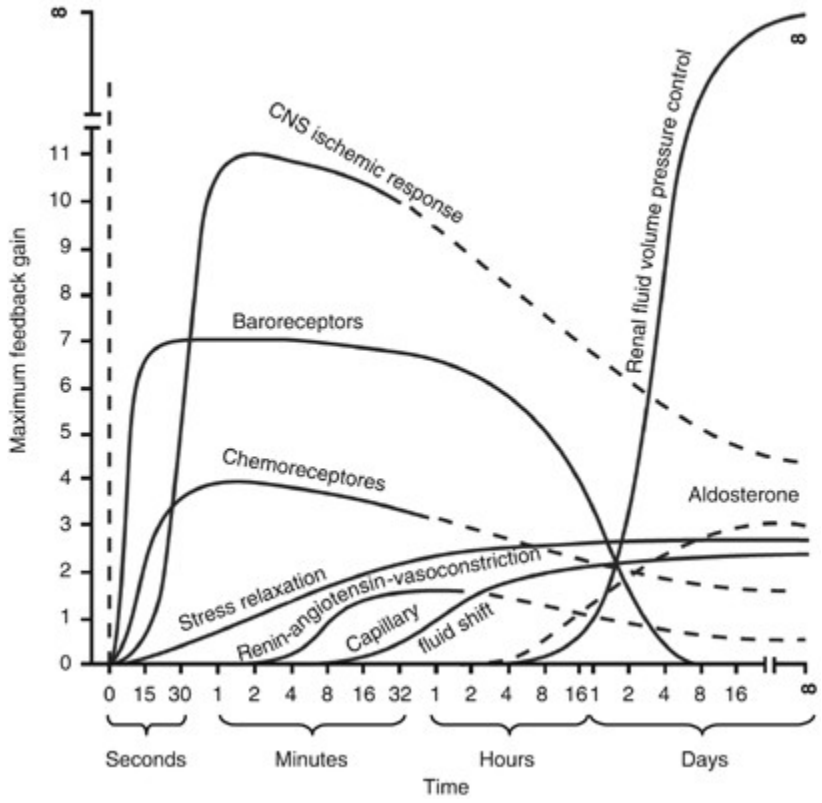


Desprez *et al.* (2019) *Toxicology in Vitro*
Vinken *et al.* (2021) *Toxicology*

Diverse time scales of biological processes in AOP



Shamir et al. SnapShot: Timescales in Cell Biology. Cell. 2016



Okumura, K., Cheng, X. Characteristics of blood pressure profiles and vascular dysfunction. *Hypertens Res* **35**, 23–24 (2012).

Risk assessment in current practice: example of ICH M3 in pharma

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

The goals of the nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, ***potential reversibility****.*

Assessments of ***withdrawal*** *can sometimes be incorporated within the design of the* ***reversibility arm*** *of a repeated-dose toxicity study.*

Perspective of systems modelling:

to build an integrated PK-MIE-**qAOP/QST system model**

To take time components into account including **(route, repeated dosing (RD)**, *ADME*, **time scales in AOP**)

To able to simulate/predict following scenarios using the **same qAOP model**

- RD exposure with dose **A** and interval **X** leads to **no adverse effect/outcome**
- RD exposure with dose **B** and interval **X** leads to **"onset" adverse effects which will recover after a sufficient recovery.**
- RD exposure with dose **B** and interval **Y** leads to **irreversible adverse effects even after a relatively long recovery.**
- **other potentials … simulate subpopulation susceptivity to certain RD exposure** scenarios

NGRA (q)AOP approach: Quantitative understanding of KERs

Quantitative AOP aim to gain quantitative understanding of KER about

- **Time-scale**
- **Response-response** relationship
- Modulating factors
- **Feedback loops**

Impact:
facilitate to classify "*Extent of quantitative understanding*" requested in Annex 2 of OECD-ENV/JM/MONO(2016)12

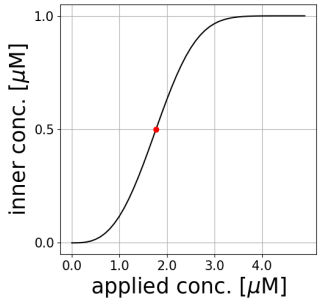
Example of KE/KERs and its quantification → activation of cellular stress pathways
Some statistics (2022):

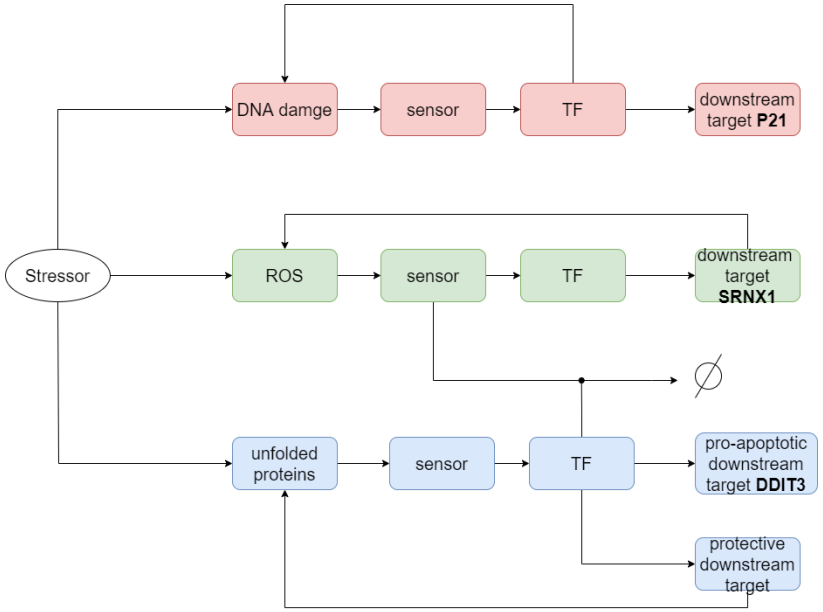
KE of oxidative stress exists in 29 AOPs in the AOPwiki.
Over 50 AOPs contain KEs related to activation of cellular stress pathways.

Quantitative systems modeling

using ordinary differential equation (ODE)

- Causality
- Mechanistic representation of biological processes
  - Homeostatic regulation
  - Cross-talk between multiple pathways
  - Quantitative representation based on law of mass action, Michaelis–Menten kinetics etc.
- *in-vitro* pharmacokinetics
  - Link the applied concentration to inner concentration (EC50)

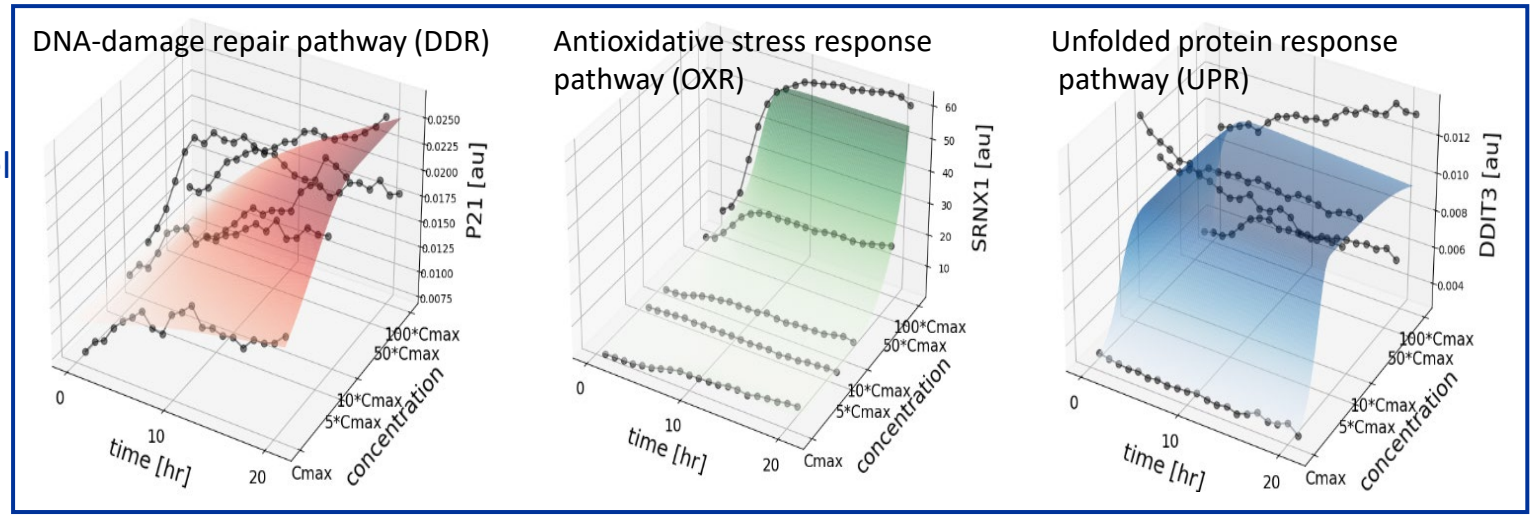




Model calibration using *in-vitro* data

Data source:
BioStudies S-BSST117 for 118 FDA-DILI labeled drugs

Representative model fitting to data of oxytetracycline



adapted from talk in SOT 2022 (Yang & Schaller)

Visualization of temporal **dose/response-response - hysteresis**

hysteresis

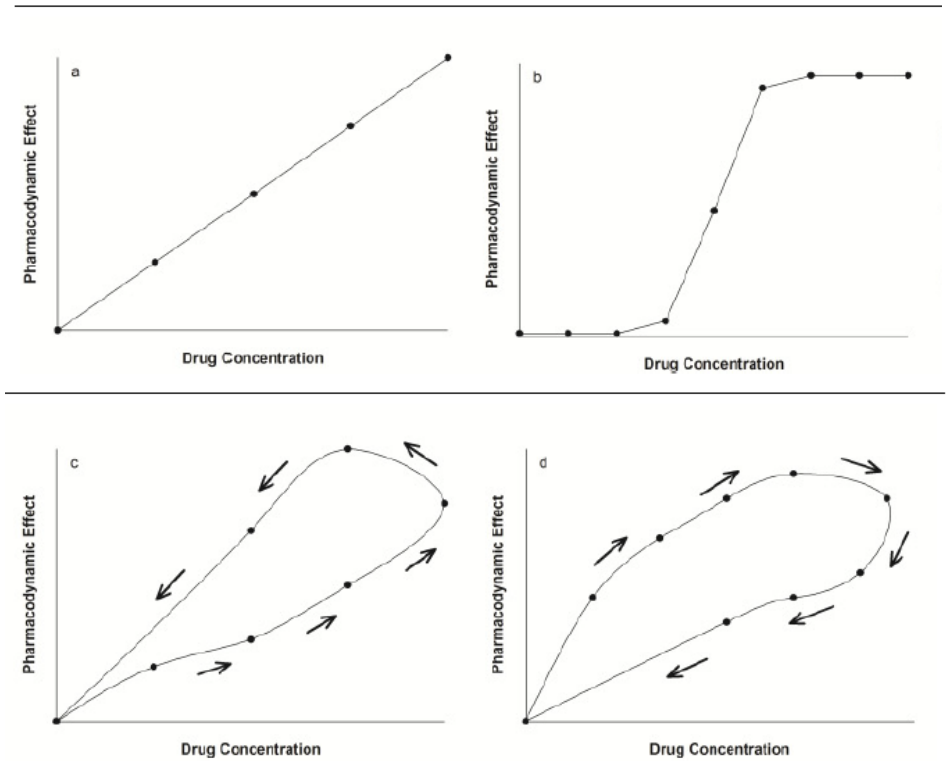


Figure 1. (a) Representation of a linear relationship between plasma concentration of a drug and measured pharmacological effect **(b)** Representation of a Sigmoidal Emax model relationship between plasma concentration of a drug and measured pharmacological effect **(c)** Representation of counter-clockwise hysteresis between plasma concentration and measured pharmacological effect **(d)** Representation of clockwise hysteresis between plasma concentration and measured pharmacological effect.

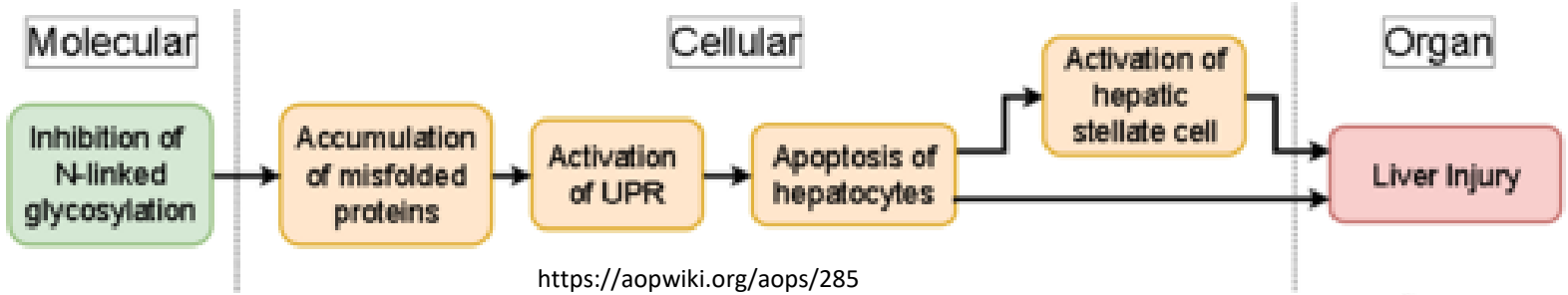
Table 1. Mechanistic Explanations for Hysteresis

Counter-clockwise Hysteresis	**Clockwise Hysteresis**
Sensitization (up regulation of receptors)	Tolerance (down regulation "desensitation" of receptors)
Input rate	Input rate
Distribution delay into the site of Effect	Disequilibrium between arterial and venous concentrations
Active agonist metabolite	Active antagonistic metabolite
Indirect effect(positive input or negative output)	Indirect effect (negative input or positive output)
Slow receptor kinetics	Feedback regulation
Time dependent protein binding	Time dependent protein binding
Racemic drugs and non-stereospecific assays	Racemic drugs and non-stereospecific assays

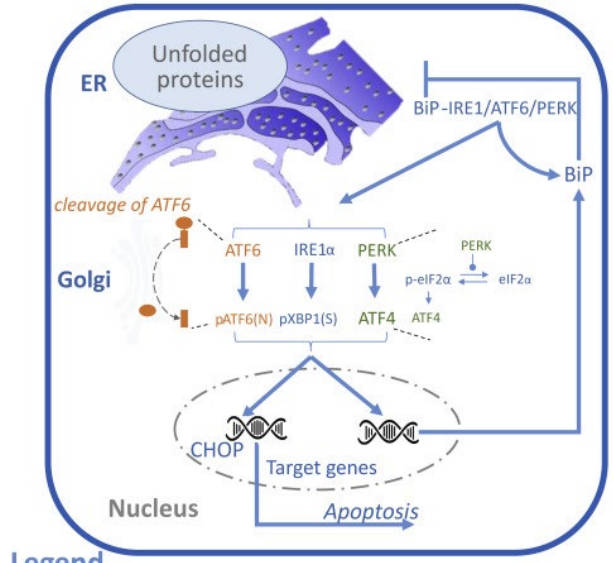
Louizos et al. Understanding the hysteresis loop conundrum in pharmacokinetic/pharmacodynamic relationships. J Pharm Pharm Sci. 2014

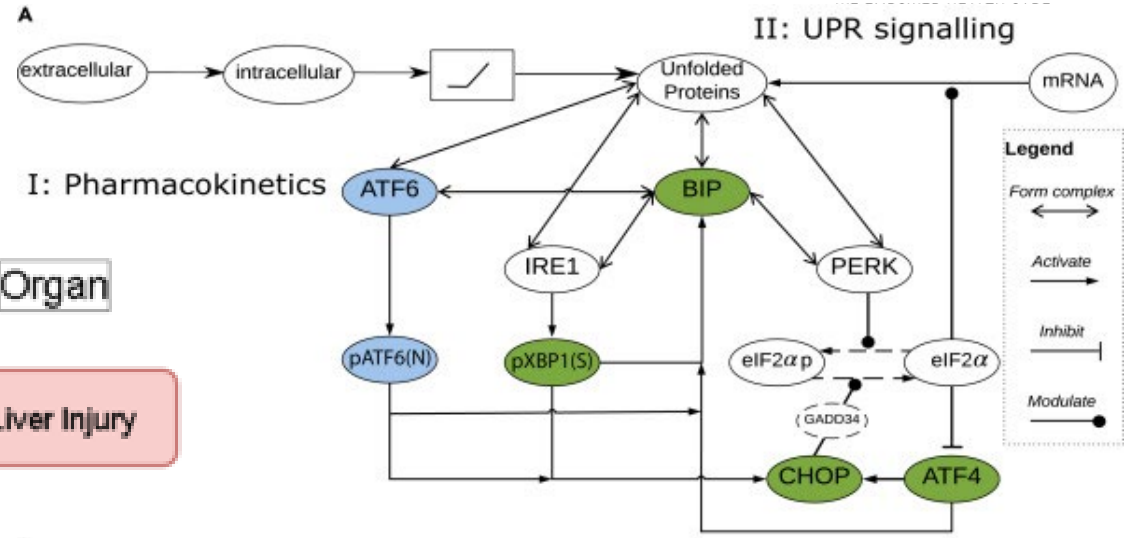
Hysteresis in qAOP:

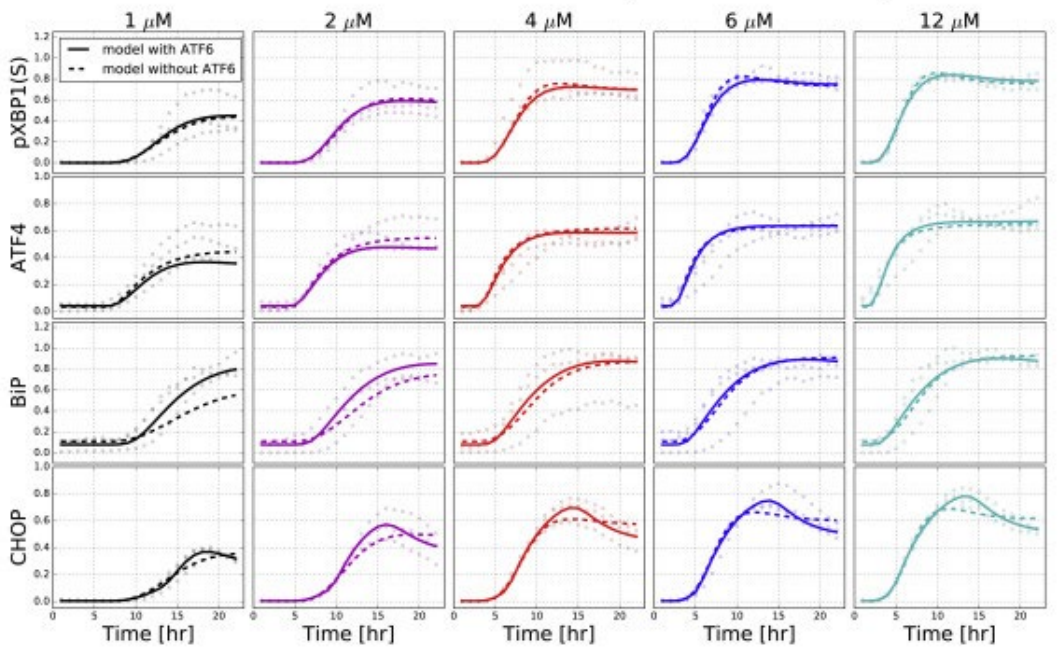
AOP: Inhibition of N-linked glycosylation leads to liver injury



https://aopwiki.org/aops/285







Yang et al. ATF6 Is a Critical Determinant of CHOP Dynamics during the Unfolded Protein Response. iScience. 2020

hysteresis plot about response-response

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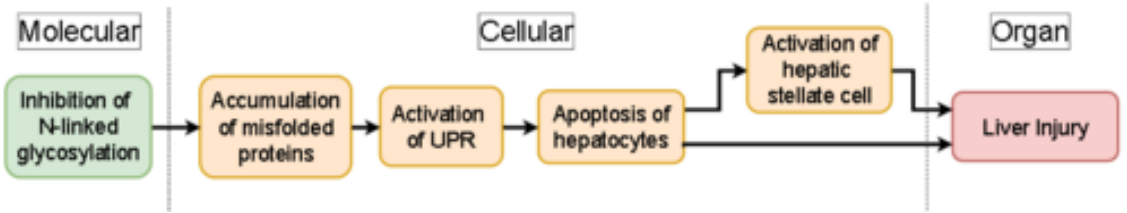
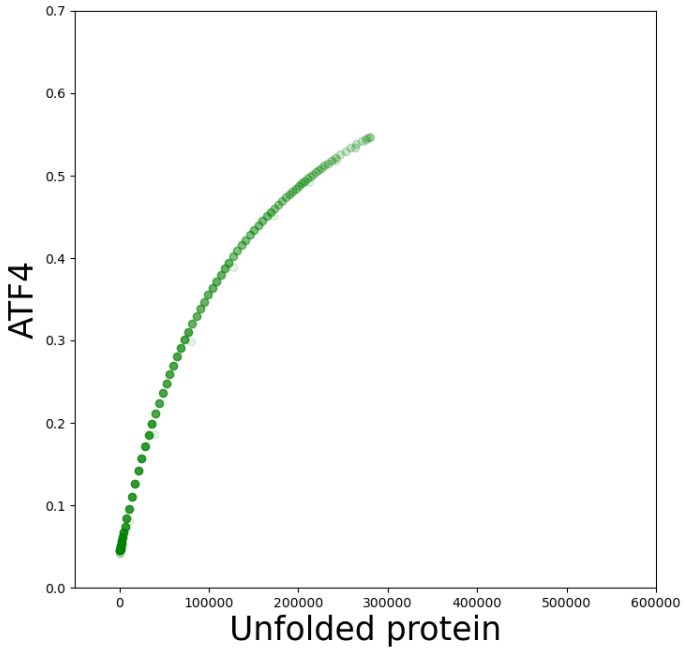
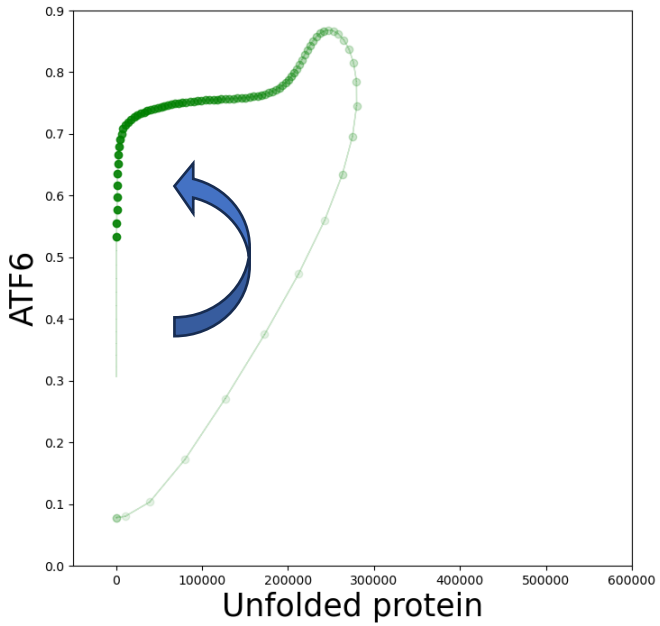
with 4 µM of tunicamycin treatment

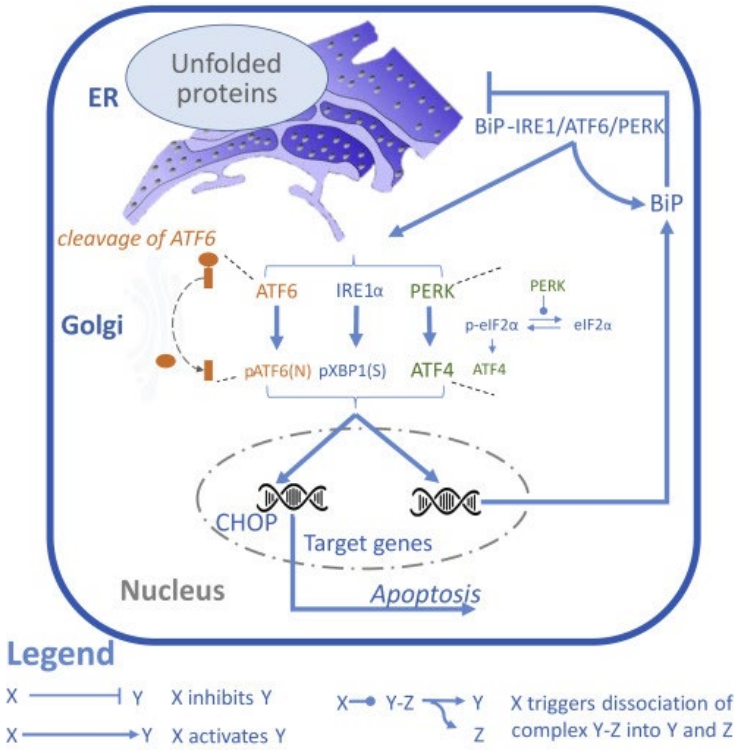




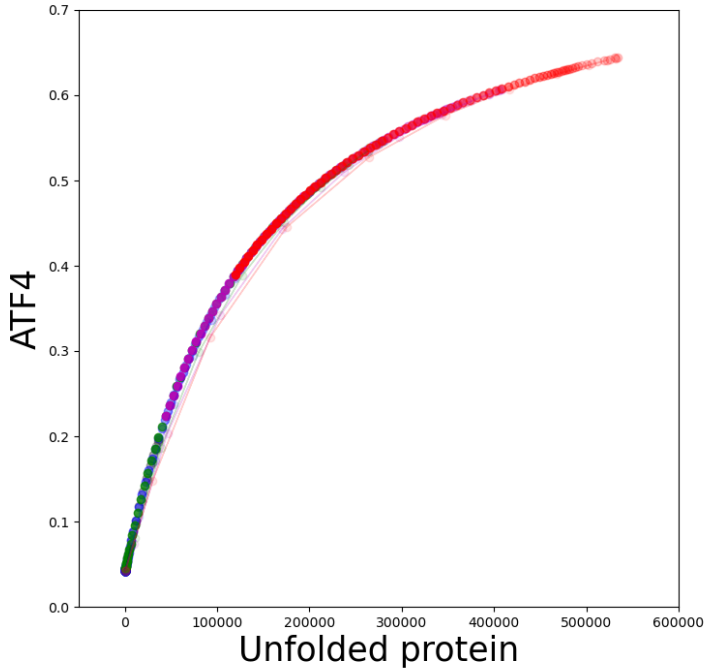
NO hysteresis

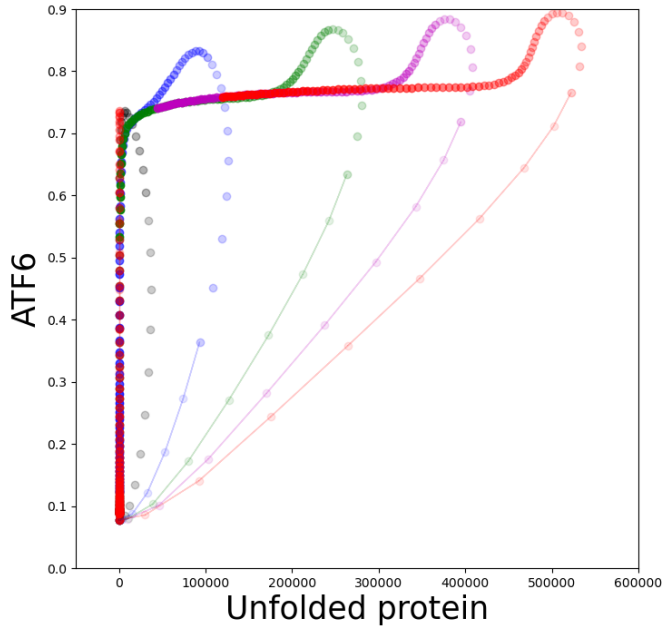


Clear hysteresis



adaptive and adverse paths/branches





Biochemical Pharmacology
Volume 190, August 2021, 114591

Integration of temporal single cell cellular stress response activity with logic-ODE modeling reveals activation of ATF4-CHOP axis as a critical predictor of drug-induced liver injury

Lukas Surya Wijaya [a 1], Panuwat Trairatphisan [b 1], Attila Gabor [b], Marije Niemeijer [a], Jason Keet [a], Ariadna Alcalà Morera [a], Kirsten E. Snijders [a], Steven Wink [a], Huan Yang [a], Stefan Schildknecht [d], James L. Stevens [a], Peter Bouwman [a], Hennicke Kamp [e], Jan Hengstler [f], Joost Beltman [a], Marcel Leist [d], Sylvia Le Dévédec [a], Julio Saez-Rodriguez [b c], Bob van de Water [a]

Yang et al. ATF6 Is a Critical Determinant of CHOP Dynamics during the Unfolded Protein Response. iScience. 2020

Conclusions

- Systems modelling of qAOP can integrate (PB)PK model to evaluate exposure-dose response relationship
- Integration of (temporal) in vitro NAM data with quantitative systems models can offer mechanistic insights and can help to design/prioritize assays to speed up screening
- Systems modelling can benefit both current RA and NGRA