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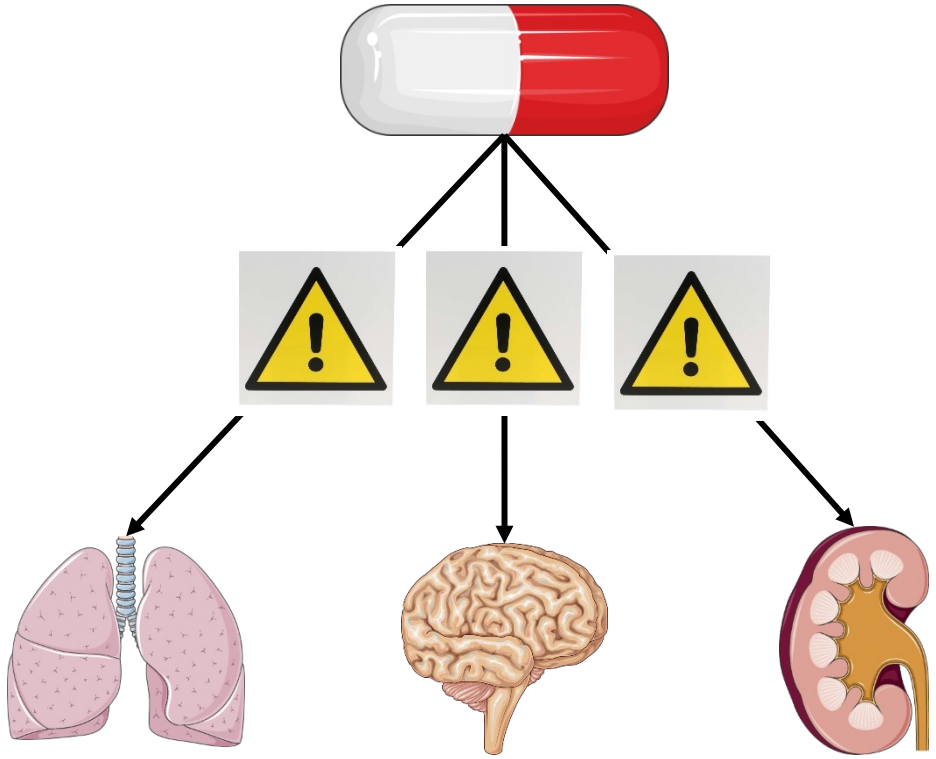
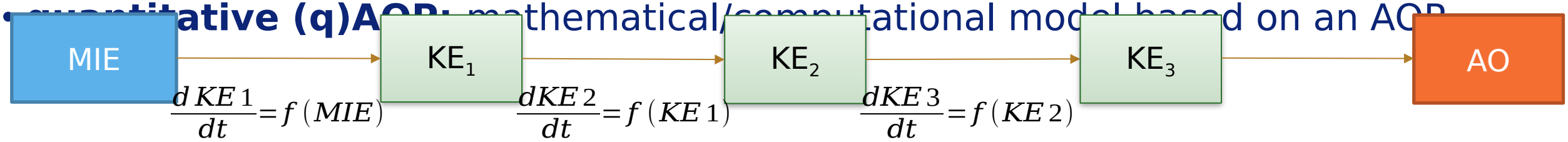
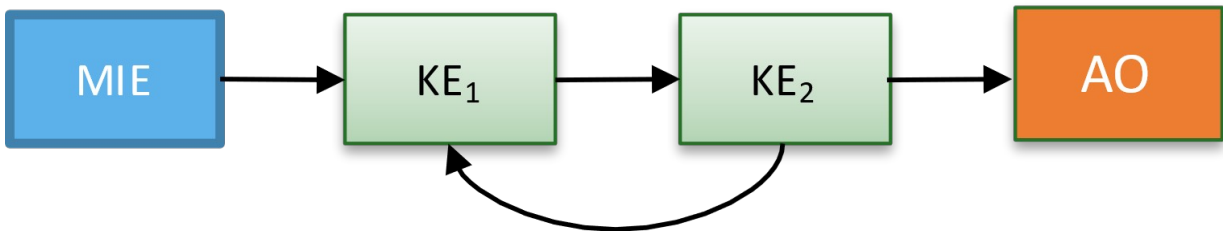
- **Drug-Induced Injury** – tissue or organ damage caused by adverse reactions or toxic metabolite of a drug.
- **Risk Assessment** – systematic process of evaluating potential adverse effects of a substance, activity, or exposure on human health or the environment.
- **Challenges** – Adversity spans through a population of patients; generalization to a group of drugs; reducing animal testing.



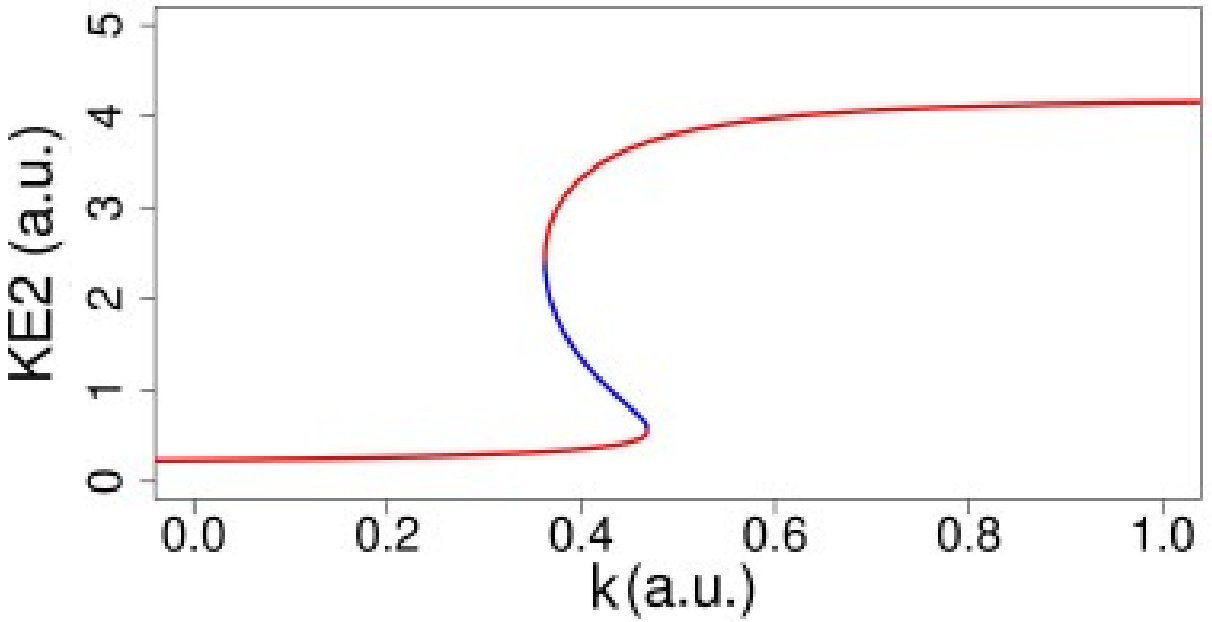
- **Adverse outcome pathway (AOP)**: sequence of key events (KEs) linking a molecular initiating event (MIE) to an adverse outcome (AO) through key event relationships (KERs);
- **quantitative (q)AOP**: mathematical/computational model based on an AOP




- **MIE** (molecular initiating event): chemical interaction between a chemical toxicant and a biological molecule.
- **KE** (key event): perturbations of the biological system at the cellular level.
- **AO** (adverse outcome): adverse effects at the tissue, organ, individual, population or ecosystem level.




AOP scheme including positive feedback loop from $KE_2$ to $KE_1$.




Bifurcation diagram related to the dose parameter *k*.

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Di Tillio, F., & Beltman, J. B. (2024). Developing quantitative Adverse Outcome Pathways: An ordinary differential equation-based computational framework. *Computational Toxicology, 32*, 100330. https://doi.org/10.1016/j.comtox.2024.100330

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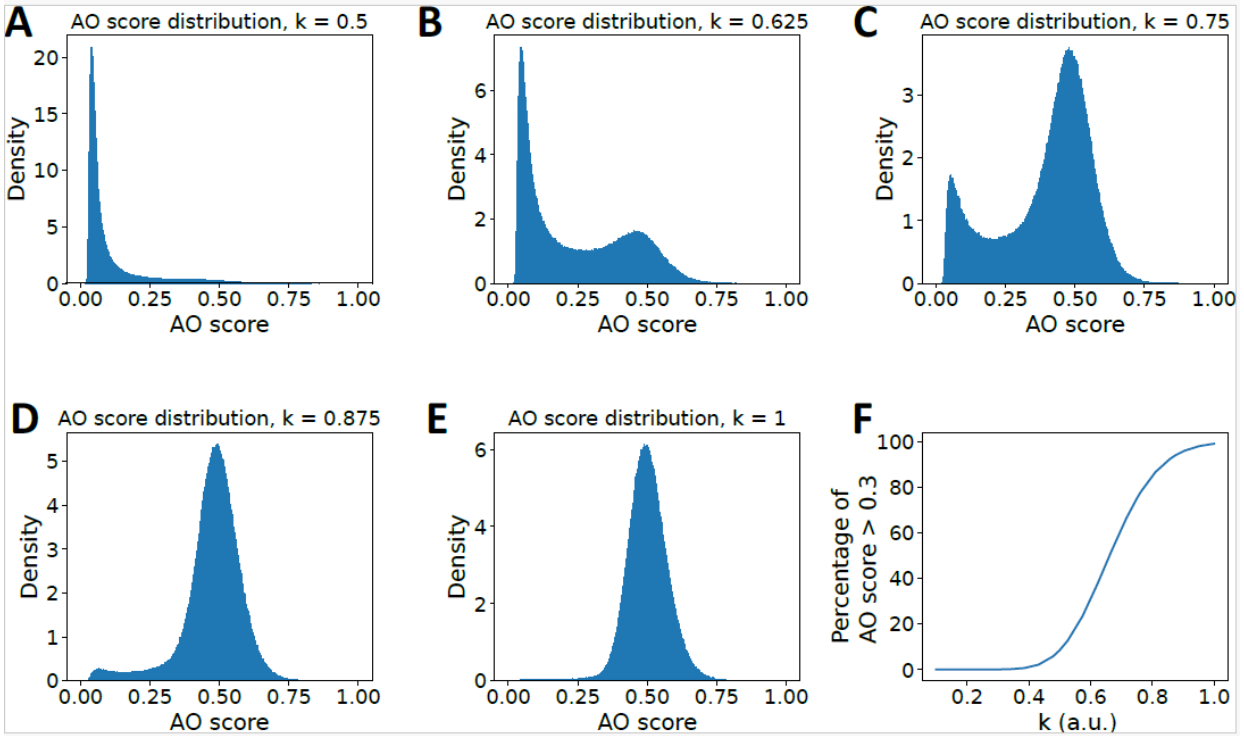
$$AOs : S_p \rightarrow [0,1]$$

$$AOs(\overline{p}) := \frac{AO_{\{t=T_{max}, \overline{p} \in S_p\}}}{max\, S_p\, AO_{\{t=T_{max}\}}}$$




The ODE-based qAOP framework provides an AO prediction over a population of patients. (A-E) AO score distribution corresponding to k=0.5 (A), k=0.625 (B), k=0.75 (C), k=0.875 (D), and k=1 (E). (F) Percentage of AO score values above a threshold of 0.3 plotted as function of k.

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Di Tillio, F., & Beltman, J. B. (2024). Developing quantitative Adverse Outcome Pathways: An ordinary differential equation-based computational framework. *Computational Toxicology, 32*, 100330. https://doi.org/10.1016/j.comtox.2024.100330

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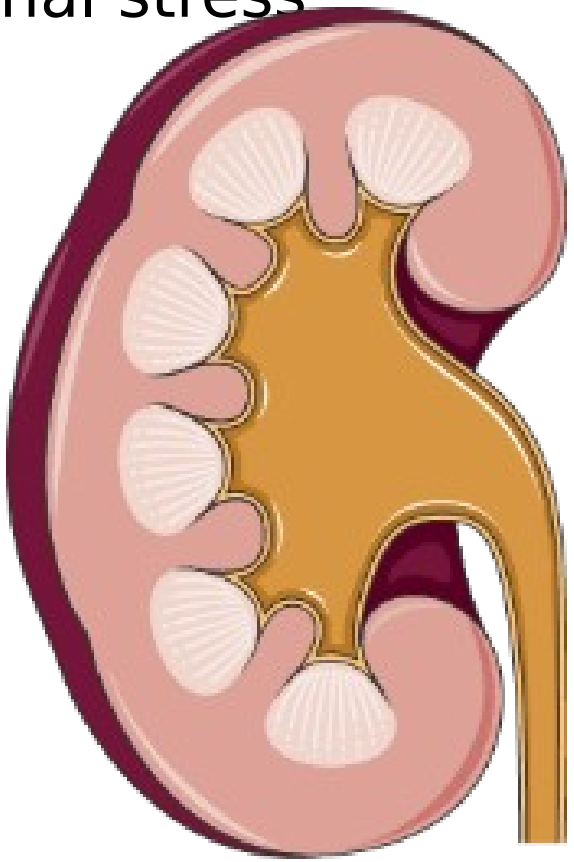
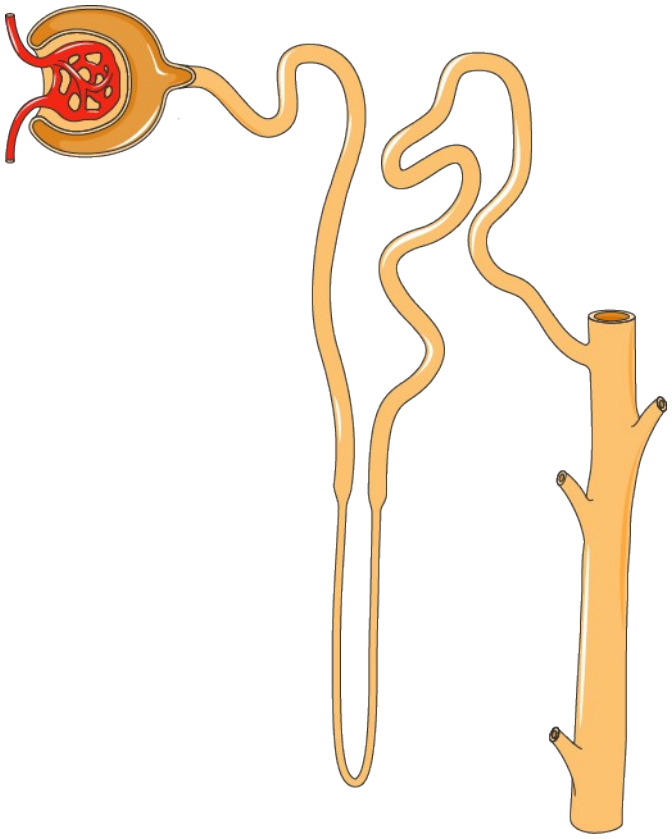
- **Nephrotoxicity**: deterioration in **kidney** function caused by drugs and external stress



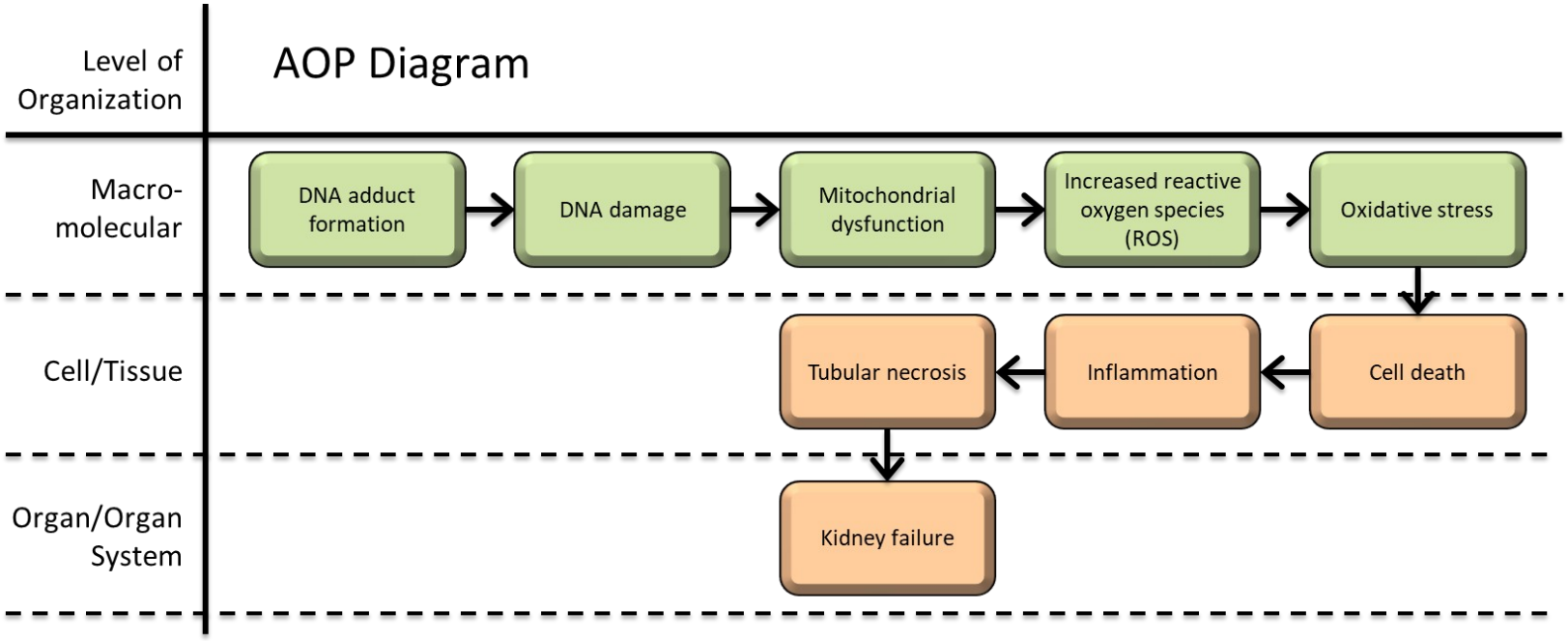
Kidney



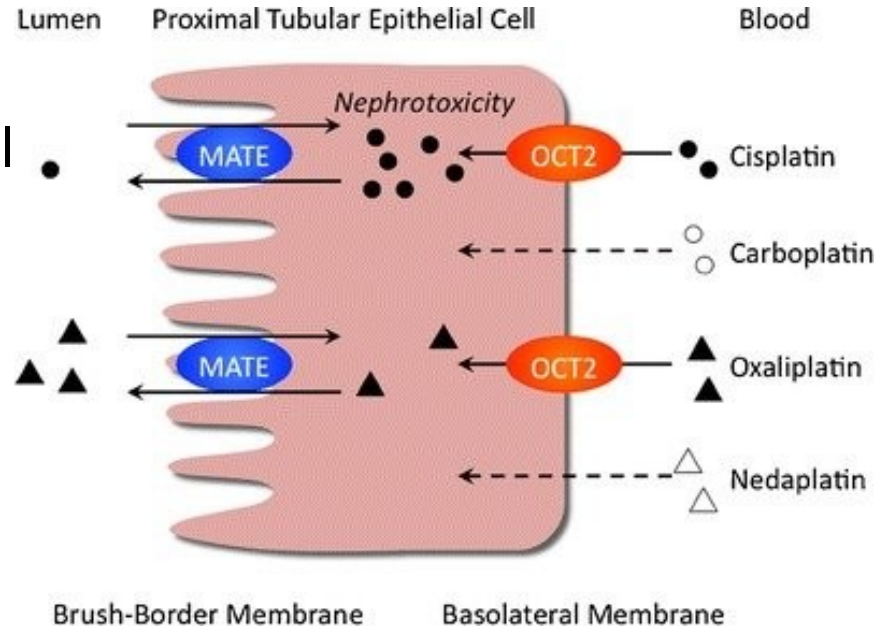
Nephron

- Platinum-based drugs (**Cisplatin**, Carboplatin, Nedaplatin, Oxaliplatin, …) are used in cancer treatment

- Similar **mechanism of action** across platinum drugs: cell aquation, **DNA binding and adduct formation**




https://aopwiki.org/aops/472

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Motohashi, H., Inui, Ki. Organic Cation Transporter OCTs (SLC22) and MATEs (SLC47) in the Human Kidney. *AAPS J* **15**, 581–588 (2013). https://doi.org/10.1208/s12248-013-9465-7

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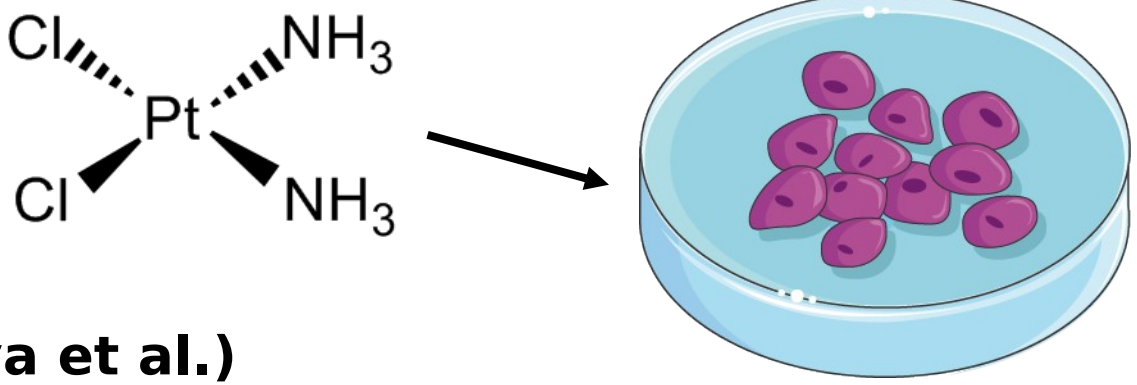
**1. In Vitro Cisplatin Data (RPTEC/TERT1 Ce**

Time-course **gene expression** TempO-Seq dat

Cell death quantified via **propidium iodide (P**




**2. In Vivo Cisplatin Data (Rat Study - Wijaya et al.)**

Time-course **transcriptomics, histopathology**, and **platinum kinetics** data.

Transcriptomics (TempO-Seq) Focused on outer-medulla proximal tubules (OMPTs).

Histopathology: Expert scoring of H&E-stained kidney images in severity categories:

Absent, Minimal, Mild, Moderate, Marked.



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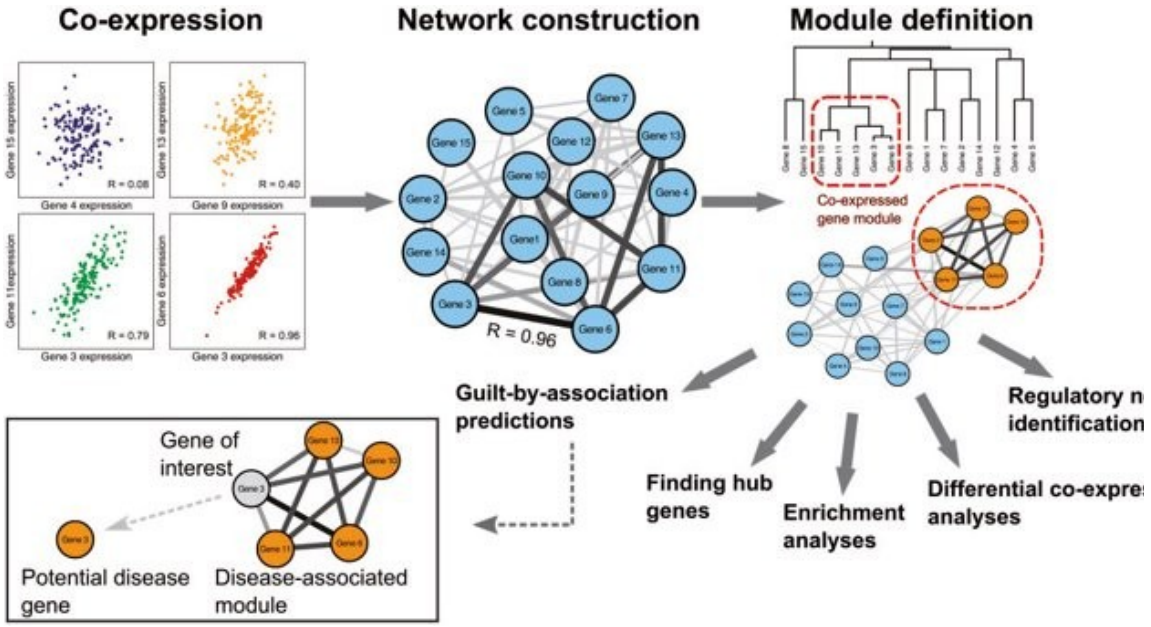
- TXG-MAPr based approach applied to transcriptomics data mapping

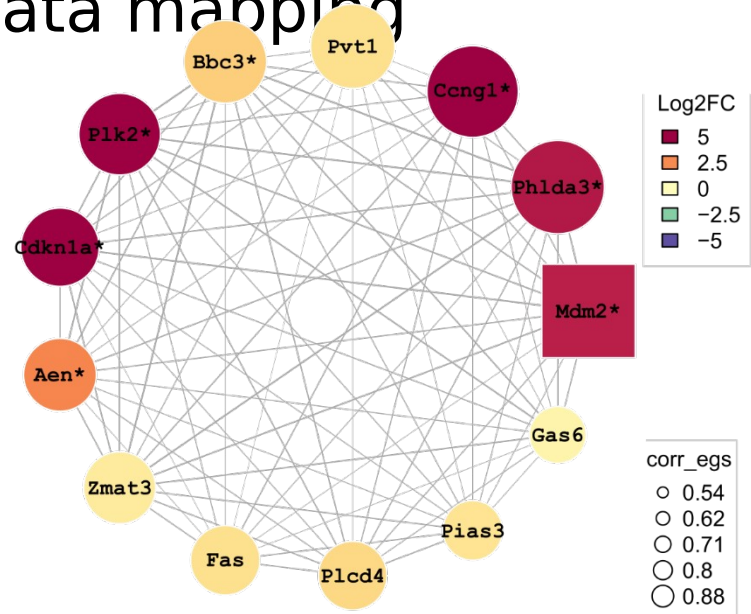



Brief Bioinform. (2018), 19: 575-592 - van Dam *et al.*

$$\text{Scaled-score} = \frac{log2FC}{SD(log2FC)} \cdot corEG$$

$$\text{Z-score} = \frac{log2FC - \overline{log2FC}}{SD(log2FC)} \cdot corEG$$

$$\text{EGs} = \frac{\sum_{k=1}^{n} Scaled-score_k}{SD(allZ-scores)}$$




Module rKID160, mapping «DNA Damage»

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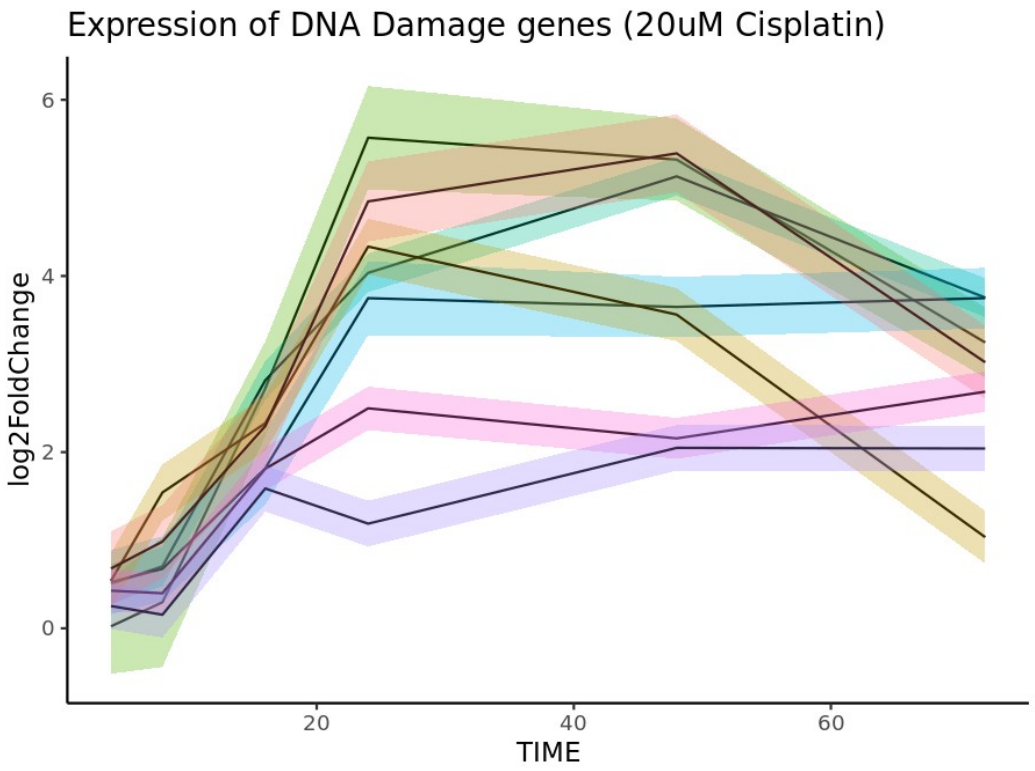


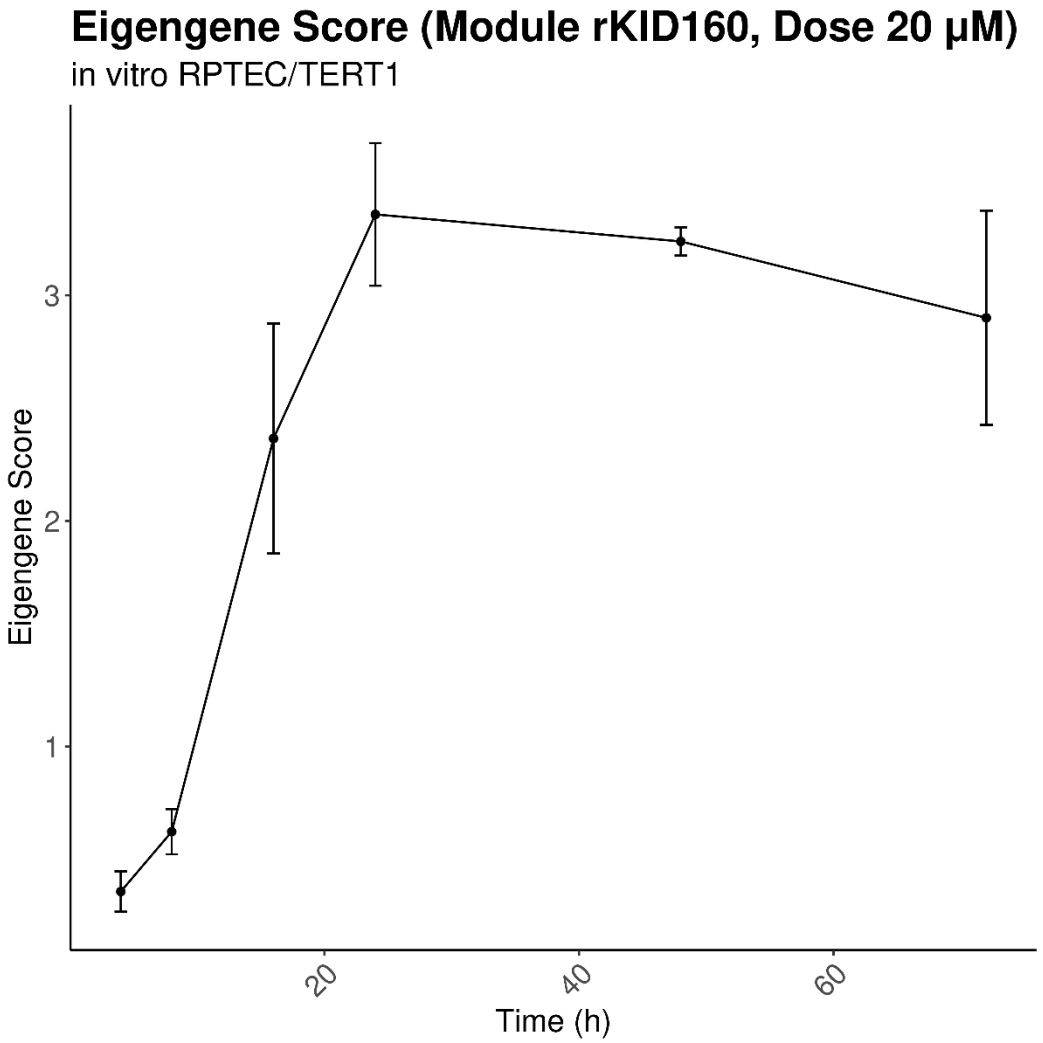


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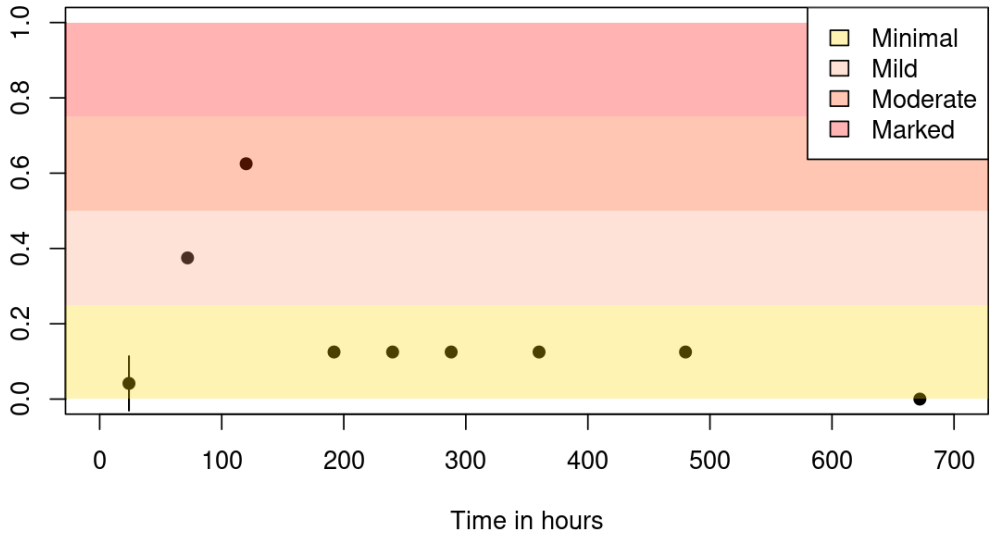
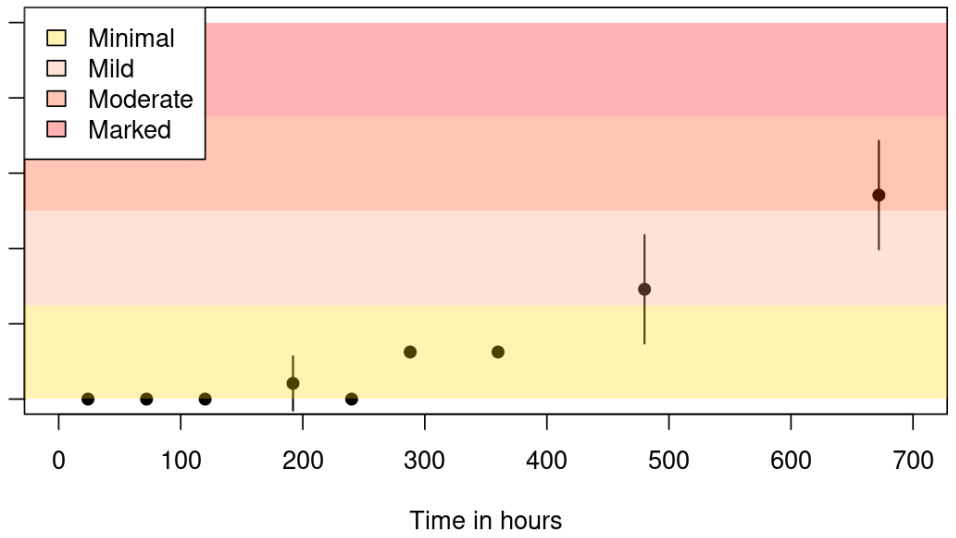
- Handling of qualitative scoring of in vivo rat histopathology data

| Renal tubular findings | Grade / Day | 1 | 2 | 4 | 6 | 9 | 11 | 13 | 16 | 21 | 29 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Necrosis | absent | 3 | 2 | | | | | | | | 3 |
| | minimal | | 1 | | | 3 | 3 | 3 | 3 | 3 | |
| | mild | | | 3 | | | | | | | |
| | moderate | | | | 3 | | | | | | |
| | marked | | | | | | | | | | |
| Fibrosis | absent | 3 | 3 | 3 | 3 | 2 | 3 | | | | |
| | minimal | | | | | 1 | | 3 | 3 | 1 | |
| | mild | | | | | | | | | 2 | 1 |
| | moderate | | | | | | | | | | 2 |
| | marked | | | | | | | | | | |

**Necrosis, 5mg/kg cisplatin**




**Fibrosis, 5mg/kg cisplatin**




**Absent** $y = 0$
**Minimal** $0 < y \leq 0.2$
**Mild** $0.25 < y \leq 0.5$
**Moderate** $0.5 < y \leq$
**Marked** $0.75 < y \leq$

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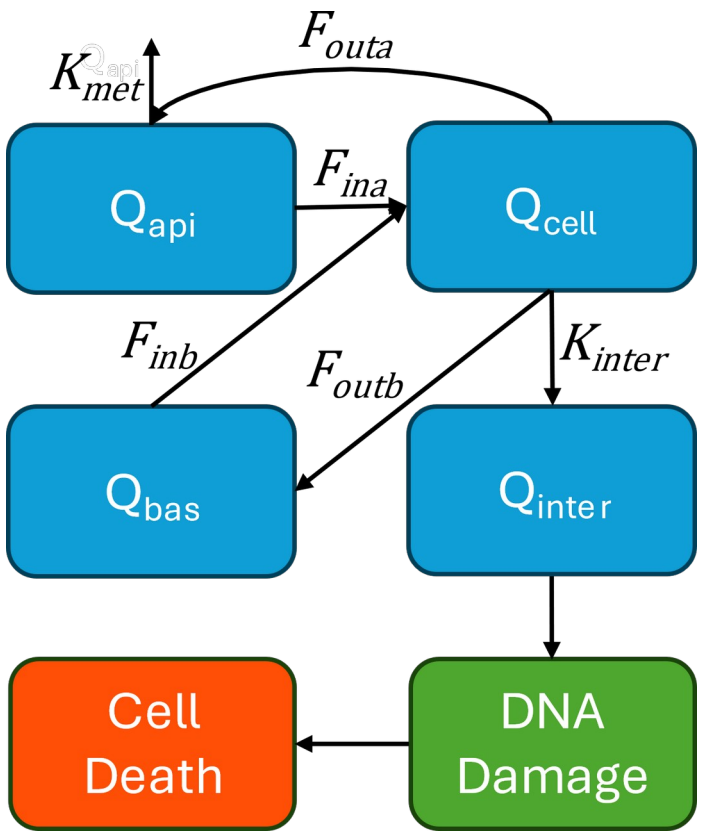
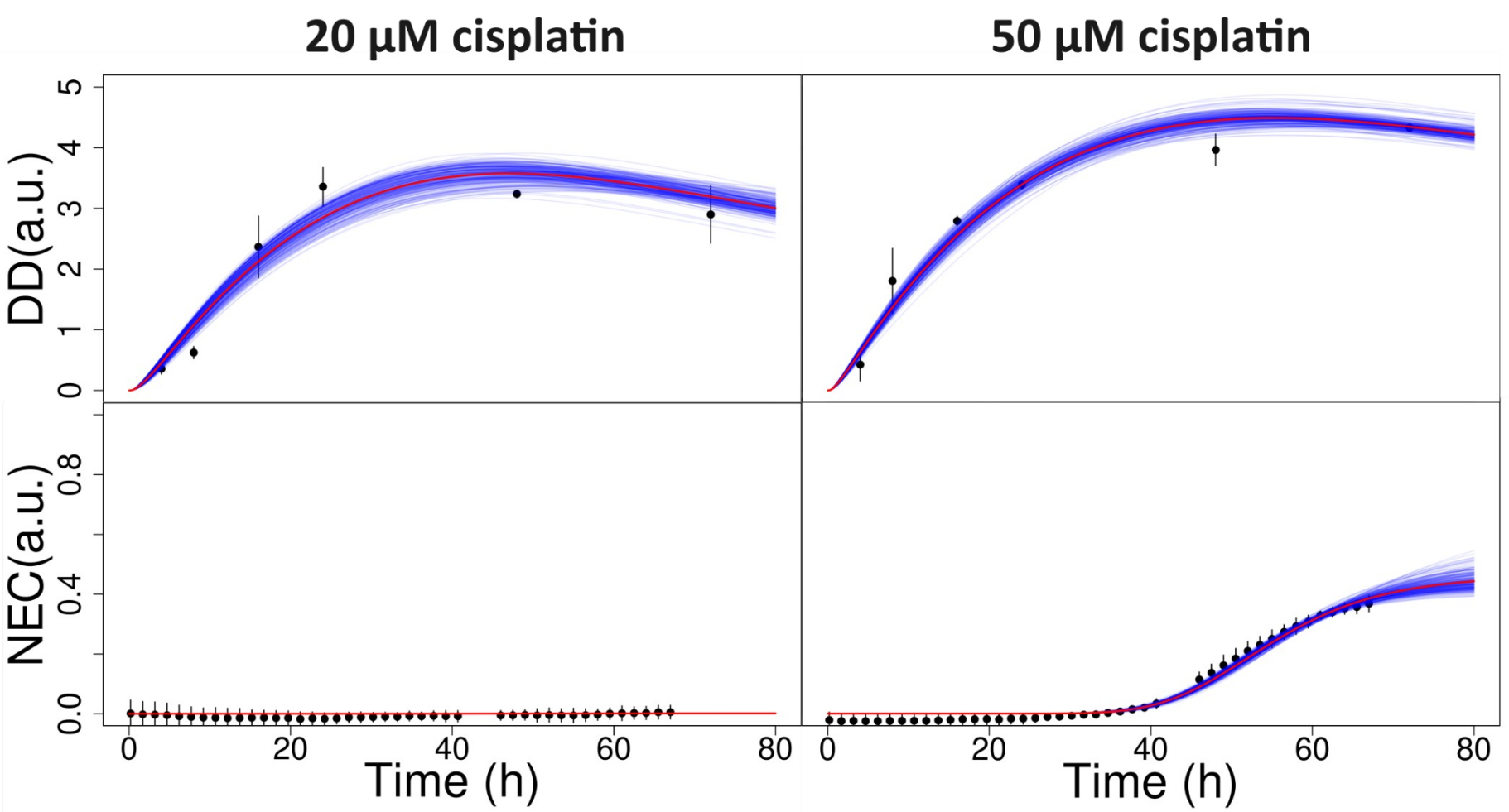



MIE model adapted from Wilmes A et al. (2015).

$$
\begin{cases}
\frac{dQ_{api}}{dt} = N_{cell} \cdot \left( F_{outa} \cdot \frac{Q_{cell}}{N_{cell} \cdot V_{cell}} - F_{ina} \cdot \frac{Q_{api}}{V_{api}} - K_{met} \cdot \frac{Q_{cell}}{N_{cell} \cdot V_{cell}} \right), \\
\frac{dQ_{bas}}{dt} = N_{cell} \cdot \left( F_{outb} \cdot \frac{Q_{cell}}{N_{cell} \cdot V_{cell}} - F_{inb} \cdot \frac{Q_{bas}}{V_{bas}} \right), \\
\frac{dQ_{cell}}{dt} = N_{cell} \cdot \left( F_{ina} \cdot \frac{Q_{api}}{V_{api}} + F_{inb} \cdot \frac{Q_{bas}}{V_{bas}} - (F_{outa} + F_{outb}) \cdot \frac{Q_{cell}}{N_{cell} \cdot V_{cell}} \right), \\
\frac{dQ_{inter}}{dt} = k_{inter} \cdot (Q_{cell} - Q_{inter}), \\
\frac{dDD}{dt} = -d_{DD} \cdot DD + \frac{k_{cDD} \cdot Q_{inter}}{k_{hillDD} + Q_{inter}}, \\
\frac{dNEC}{dt} = maxdeath \cdot \frac{DD^h}{k_{hillnec}^h + DD^h} \cdot (p - NEC). \\
Q_{api}(0) = 10^{-15} C_0 MWV_{api}, \\
Q_{bas}(0) = 10^{-15} C_0 MWV_{bas}, \\
Q_{cell}(0) = 0, \\
Q_{inter}(0) = 0, \\
DD(0) = 0, \\
NEC(0) = 0.
\end{cases}
$$

# ODE model fit to KE data

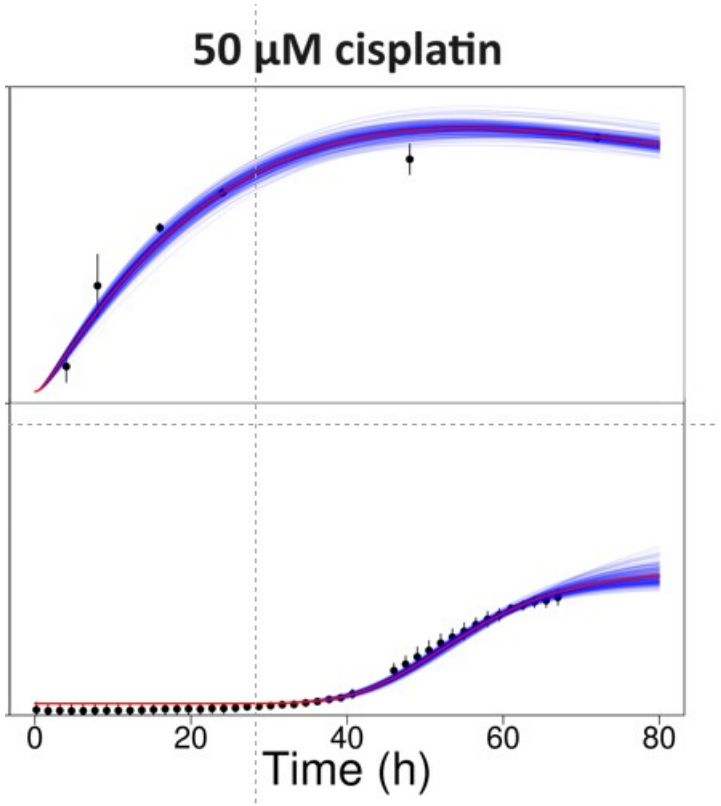



data mean ± sd

ODE model solution for specific parameter set

Mean of the sampled solutions

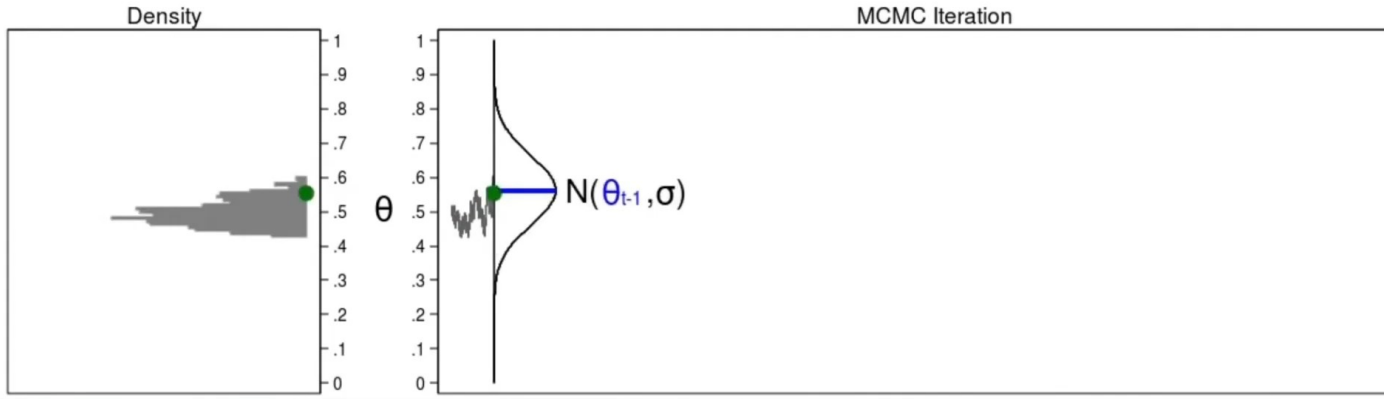
$$
\begin{cases}
\frac{dQ_{api}}{dt} = N_{cell} \cdot \left( F_{outa} \cdot \frac{Q_{cell}}{N_{cell} \cdot V_{cell}} - F_{ina} \cdot \frac{Q_{api}}{V_{api}} - K_{met} \cdot \frac{Q_{cell}}{N_{cell} \cdot V_{cell}} \right), \\
\frac{dQ_{bas}}{dt} = N_{cell} \cdot \left( F_{outb} \cdot \frac{Q_{cell}}{N_{cell} \cdot V_{cell}} - F_{inb} \cdot \frac{Q_{bas}}{V_{bas}} \right), \\
\frac{dQ_{cell}}{dt} = N_{cell} \cdot \left( F_{ina} \cdot \frac{Q_{api}}{V_{api}} + F_{inb} \cdot \frac{Q_{bas}}{V_{bas}} - (F_{outa} + F_{outb}) \cdot \frac{Q_{cell}}{N_{cell} \cdot V_{cell}} \right), \\
\frac{dQ_{inter}}{dt} = k_{inter} \cdot (Q_{cell} - Q_{inter}), \\
\frac{dDD}{dt} = -d_{DD} \cdot DD + \frac{k_{cDD} \cdot Q_{inter}}{k_{hillDD} + Q_{inter}}, \\
\frac{dNEC}{dt} = maxdeath \cdot \frac{DD^h}{k_{hillnec}^h + DD^h} \cdot (p - NEC). \\
Q_{api}(0) = 10^{-15} C_0 MW V_{api}, \\
Q_{bas}(0) = 10^{-15} C_0 MW V_{bas}, \\
Q_{cell}(0) = 0, \\
Q_{inter}(0) = 0, \\
DD(0) = 0, \\
NEC(0) = 0.
\end{cases}
$$



**BAYESIAN INFERENCE**
: data

$$\max_{\theta} \{p(\theta/x)\}$$

Bayes theorem:



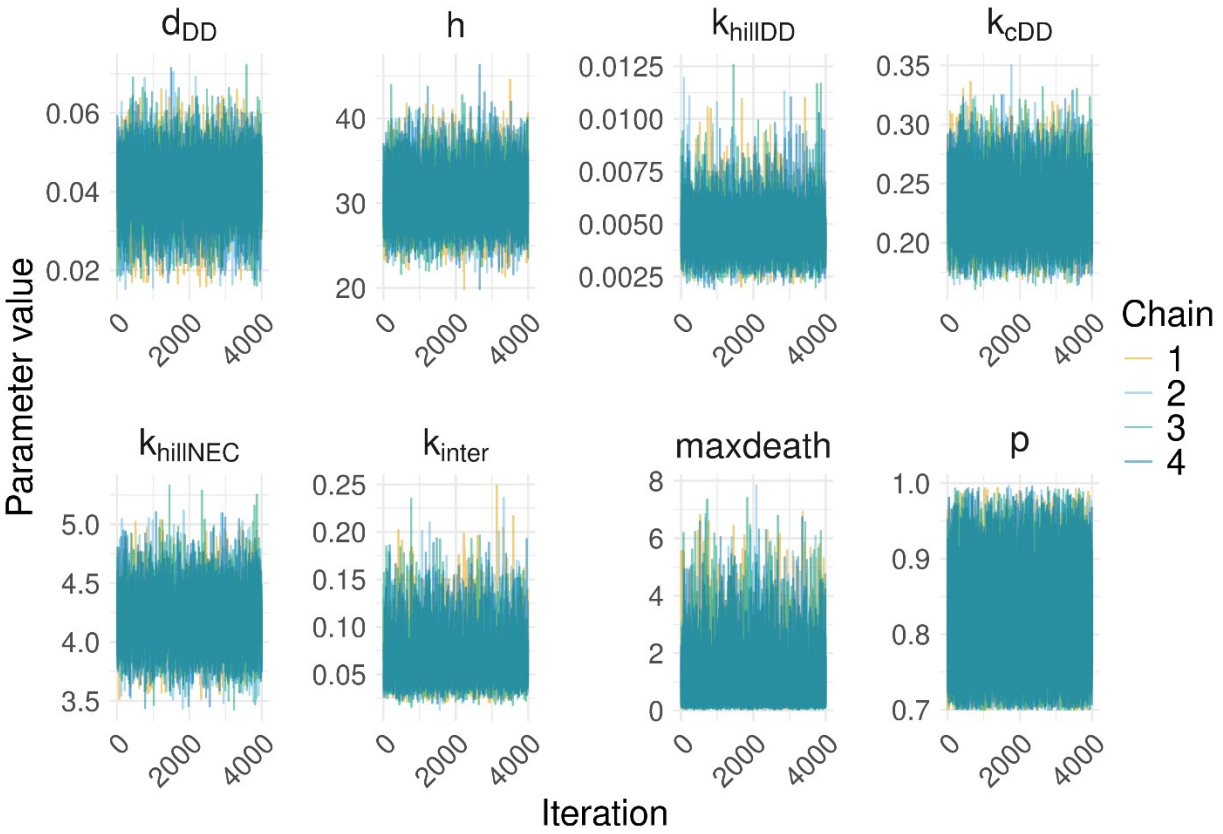

Step 1: $r(\theta_{new}, \theta_{t-1}) = \frac{\text{Posterior}(\theta_{new})}{\text{Posterior}(\theta_{t-1})} = \frac{\text{Beta}(1,1,0.286) \times \text{Binomial}(10,4,0.286)}{\text{Beta}(1,1,0.380) \times \text{Binomial}(10,4,0.380)} = 0.747$

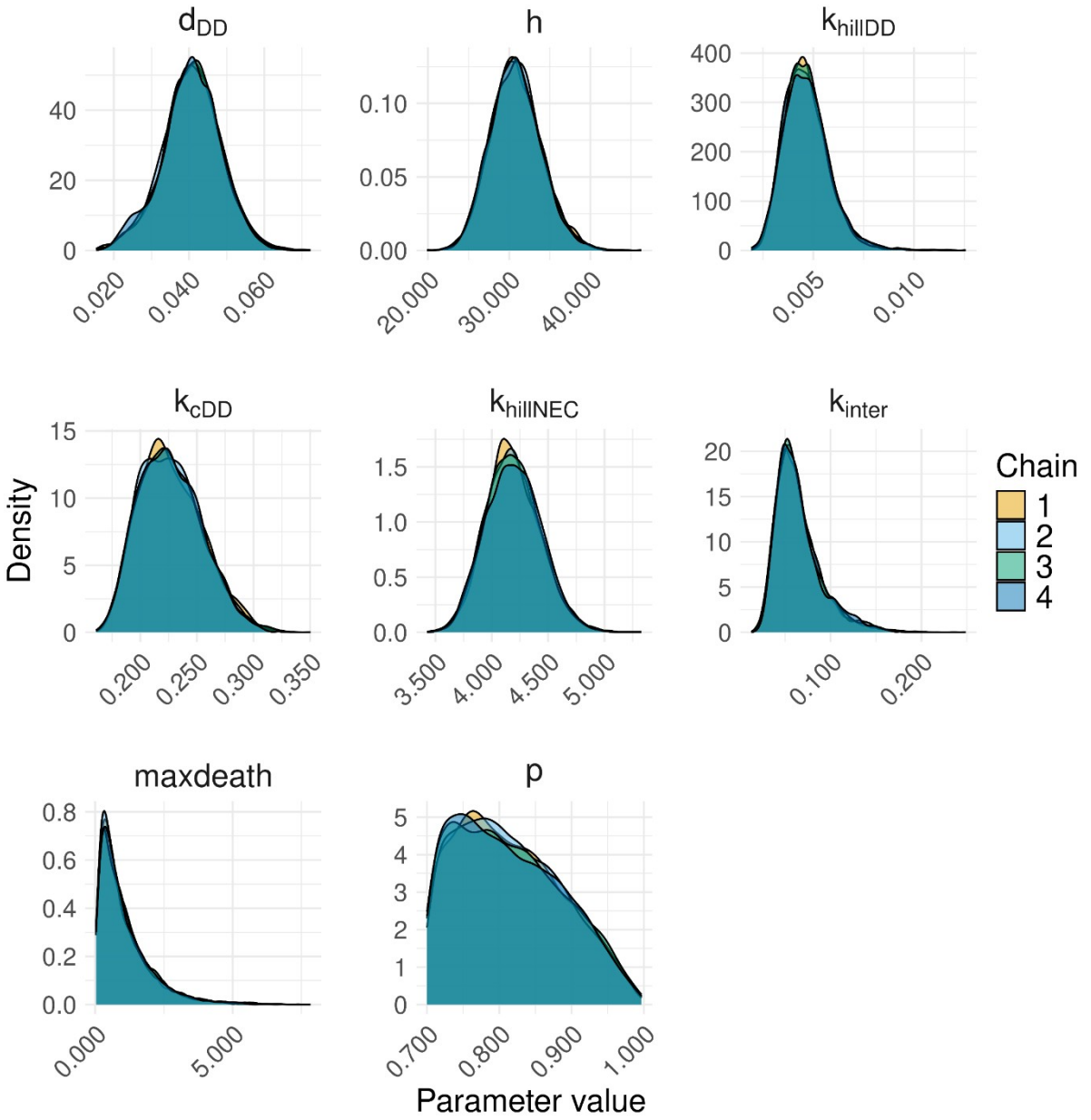
Step 2: Acceptance probability $\alpha(\theta_{new}, \theta_{t-1}) = \min\{r(\theta_{new}, \theta_{t-1}), 1\} = \min\{0.747, 1\} = 0.747$

Step 3: Draw u ~ Uniform(0,1) = 0.094

Step 4: If $u < \alpha(\theta_{new}, \theta_{t-1})$ → If $0.094 < 0.747$ Then $\theta_t = \theta_{new} = 0.286$

Otherwise $\theta_t = \theta_{t-1} = 0.380$




# Trace & posterior density plots

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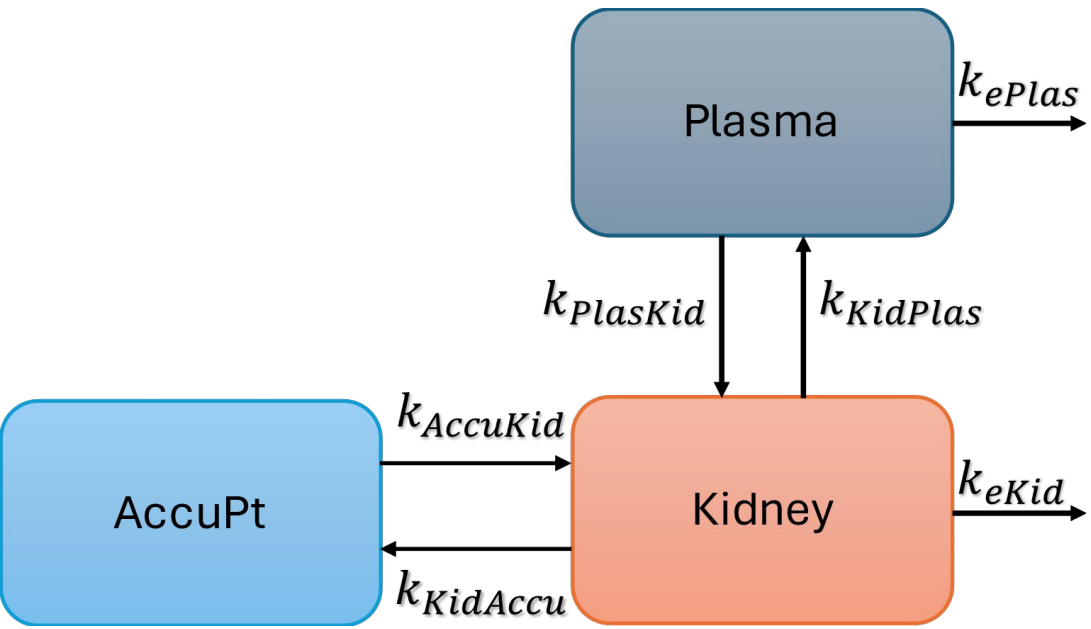
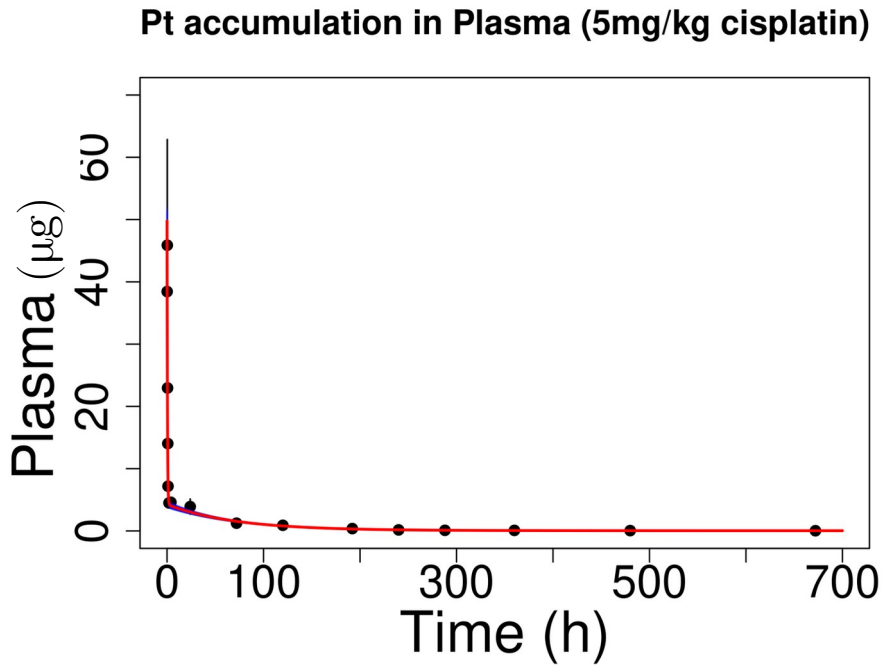
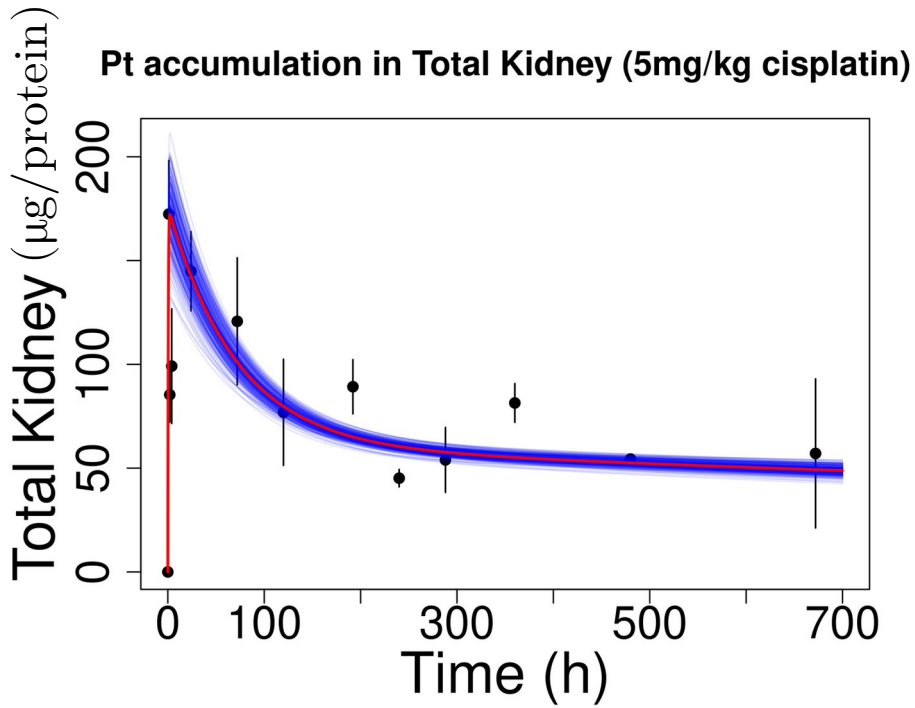
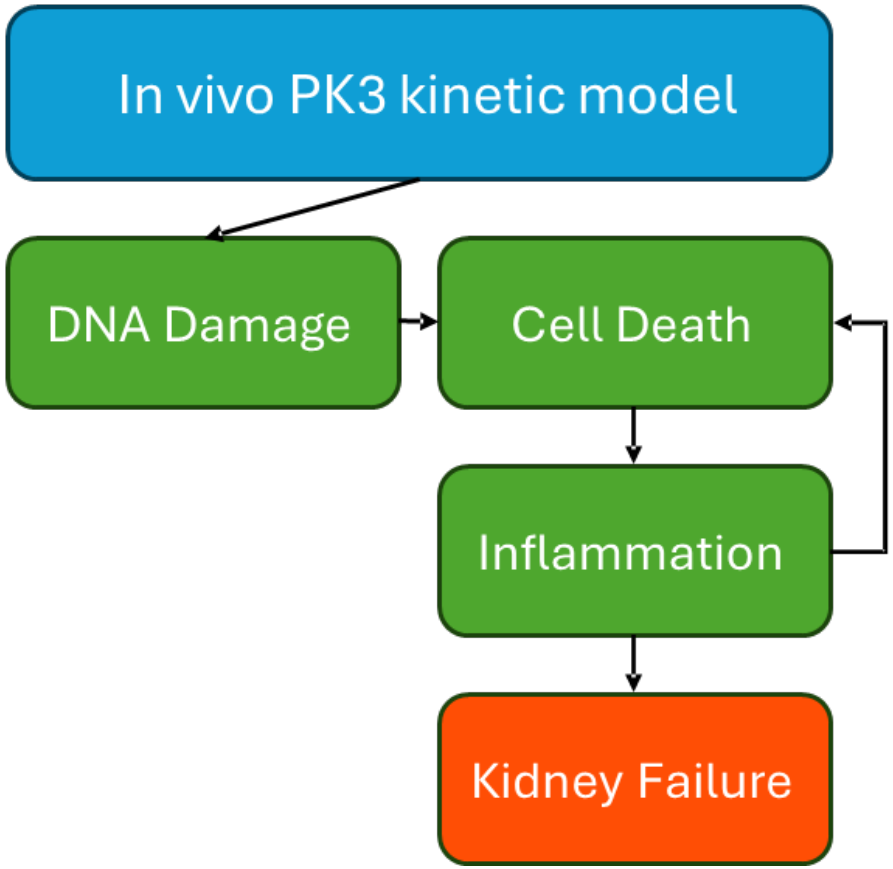
$$
\begin{cases}
\dfrac{dPlasma}{dt} = k_{KidPlas}KidneyPt - (k_{PlasKid} + k_{eplas})Plasma, \\
\dfrac{dKidneyPt}{dt} = k_{accukid}AccuPt + k_{PlasKid}Plasma - (k_{KidPlas} + k_{KidAccu} + k_{ekid})KidneyPt, \\
\dfrac{dAccuPt}{dt} = k_{KidAccu}KidneyPt - k_{accukid}AccuPt, \\
Plasma(0) = C_0, \\
KidneyPt(0) = 0, \\
AccuPt(0) = 0.
\end{cases}
$$






$$
\begin{cases}
\dfrac{dDD}{dt} = k_{kidDD}\dfrac{scale \cdot (KidneyPt + AccuPt)}{k_{hillDD} + scale \cdot (KidneyPt + AccuPt)} - d_{DD}DD, \\
\dfrac{dCD}{dt} = maxdeath\dfrac{DD^h}{k^h_{hillNEC} + DD^h}(1 - CD) - d_{CD}CD\,INF, \\
\dfrac{dINF}{dt} = k_{CDINF}CD - d_{INF}INF, \\
\dfrac{dKF}{dt} = \dfrac{k_{INFKF}INF^{p(t)+1}}{k^{p(t)+1}_{hillKF} + INF^{p+1}}(1 - KF), \\
\dfrac{dp}{dt} = -d_p p, \\
DD(0) = CD(0) = INF(0) = KF(0) = 0, \\
p(0) = 10.
\end{cases}
$$

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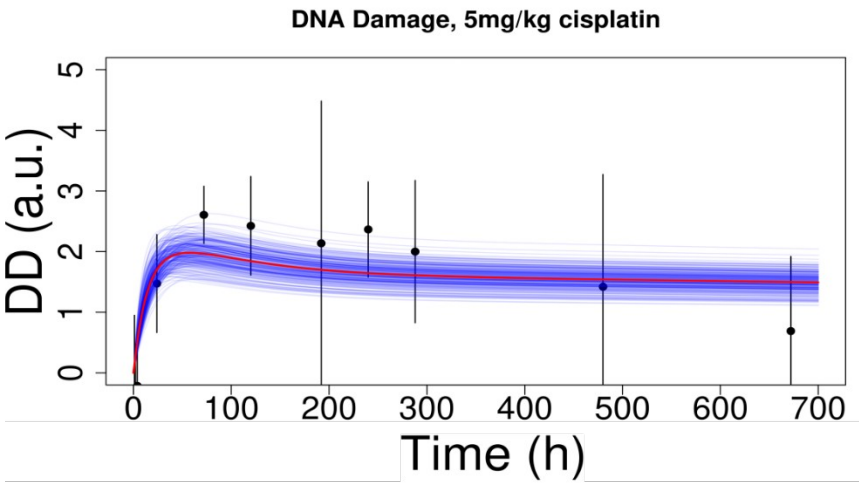
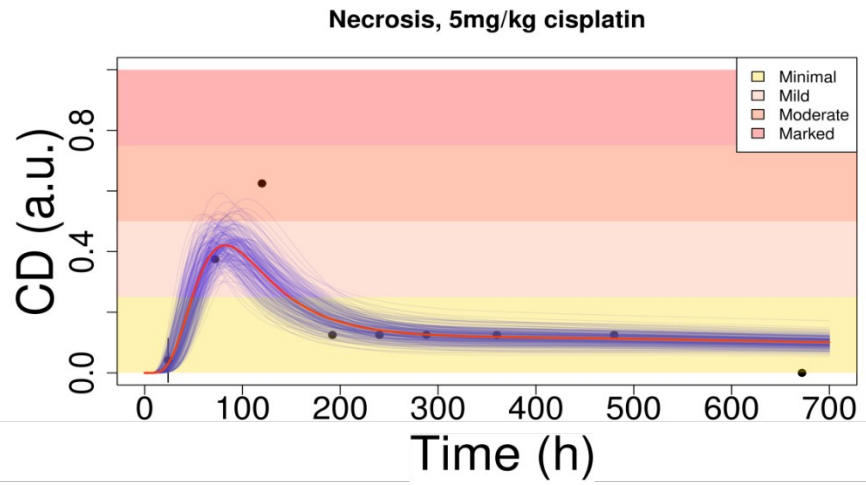
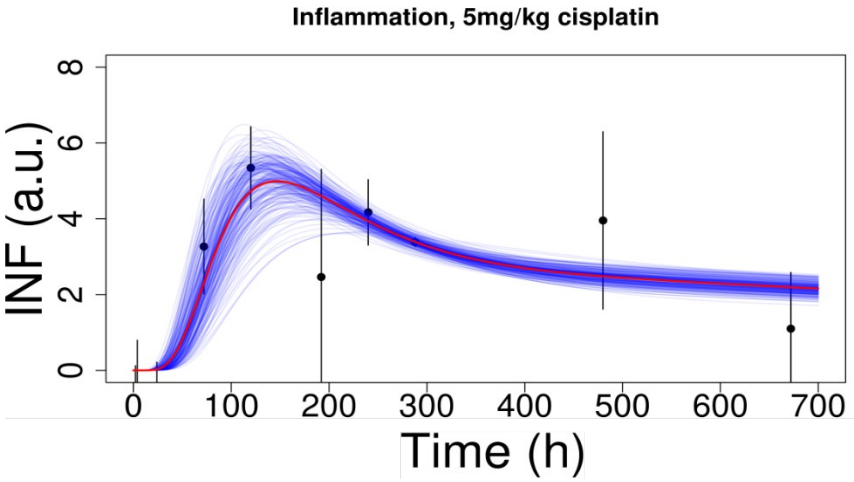
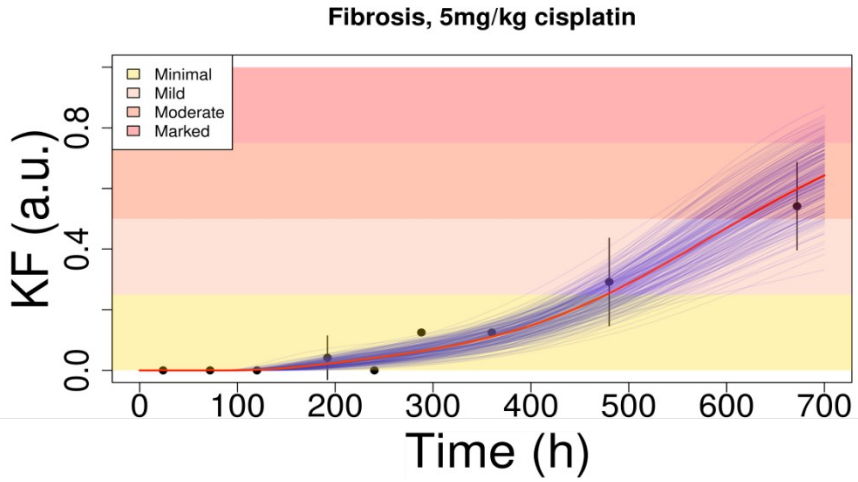


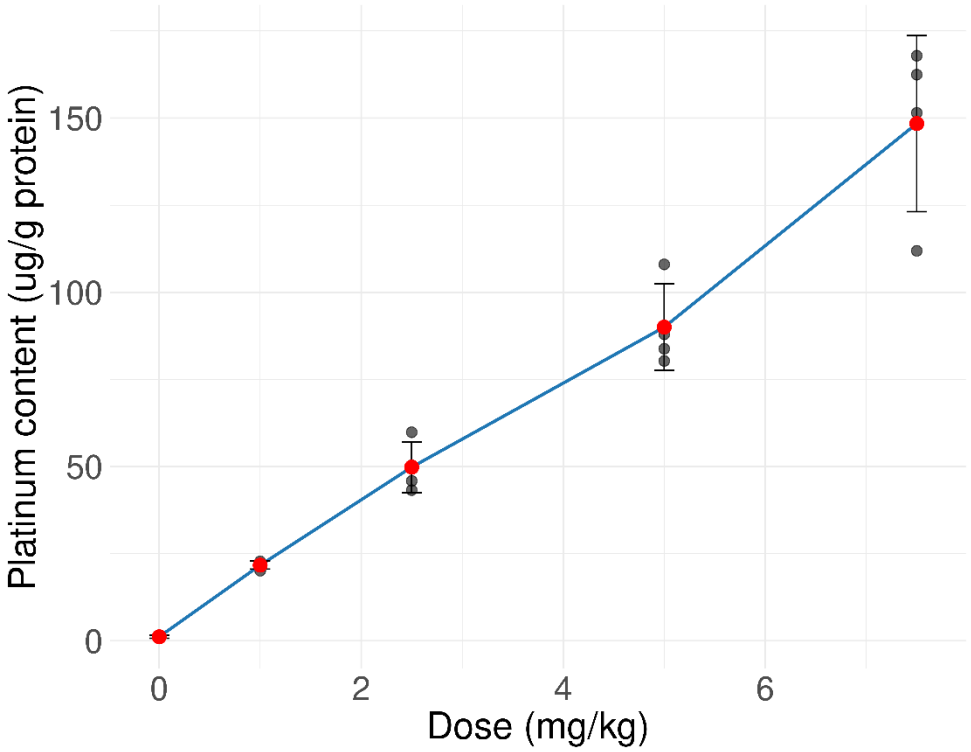



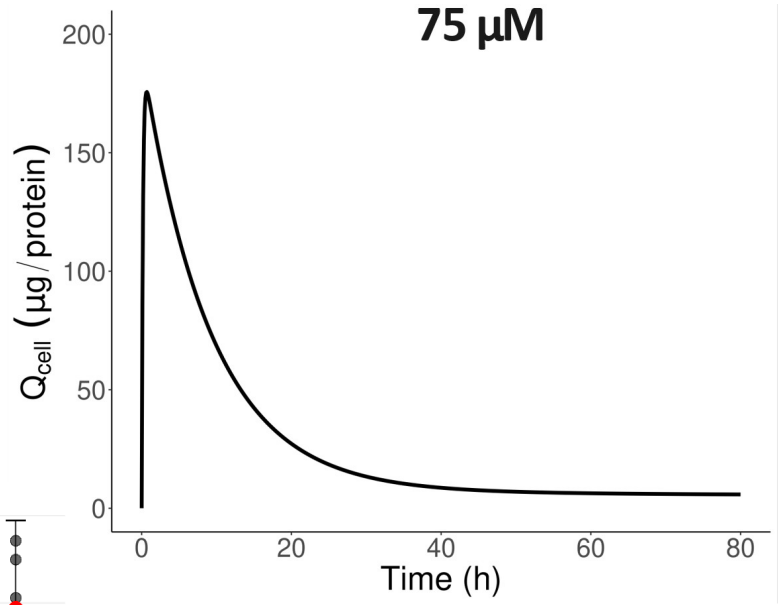



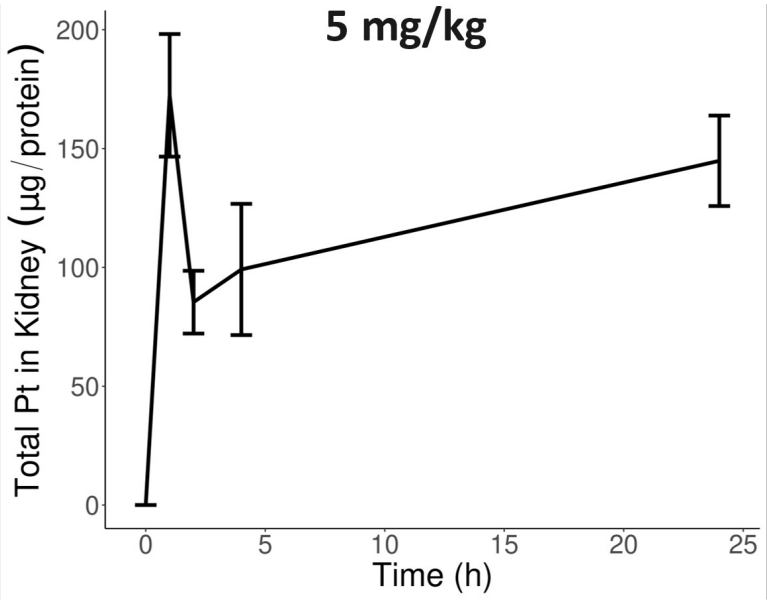




**DD**: DNA Damage; TXG-MAPr based (module active for EGs>1.5)
**CD**: Cell Death; based on Necrosis Histopathology
**INF**: Inflammation; TXG-MAPr based
**KF**: Kidney Failure; based on Fibrosis Histopathology

1) Identify in vitro dose giving comparable Cmax to the in vivo case




2) Dose-response in vivo data shows that Pt effective concentration behaves linearly in the considered dose range.

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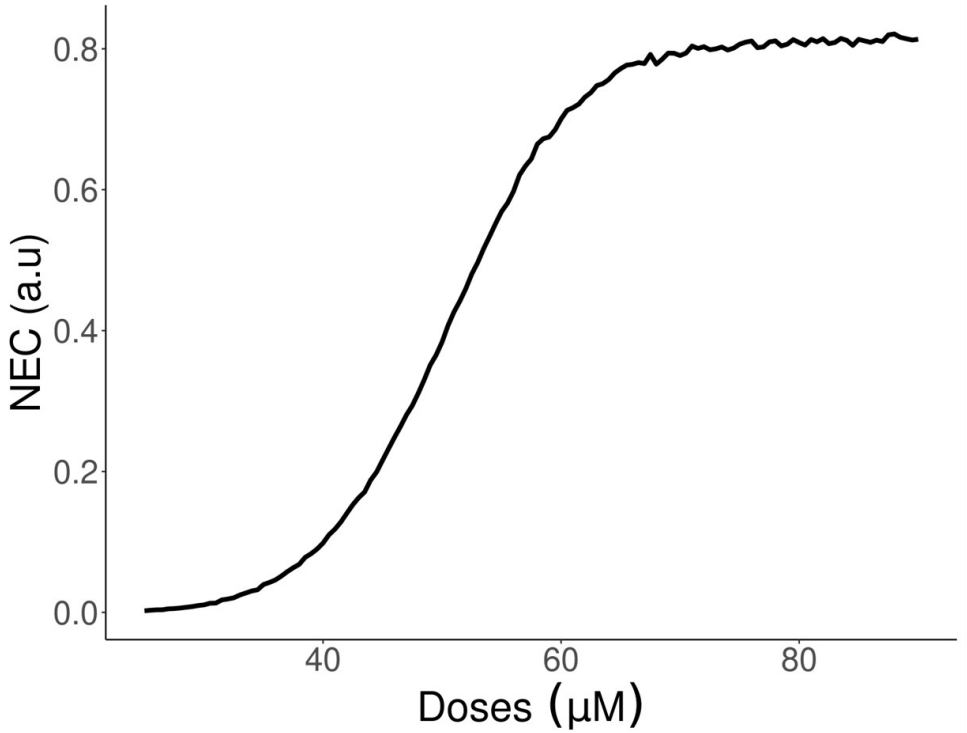


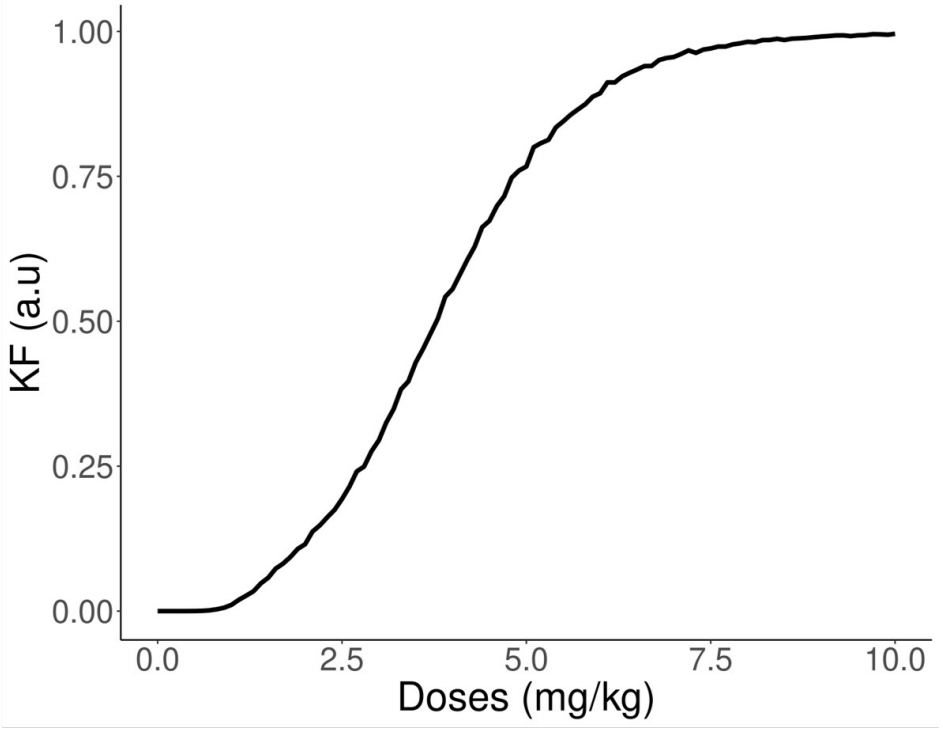


3) We can identify in vitro (20 – 90 $\mu M$) and in vivo (0 – 10 mg/kg) dose ranges causing comparable adverse outcomes.

# Cytotoxicity of *cis*-Platinum(II) Conjugate Models. The Effect of Chelating Arms and Leaving Groups on Cytotoxicity: A Quantitative Structure–Activity Relationship Approach

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Thirteen newly synthesized or resynthesized diamine–platinum(II) complexes were characterized, and their cytotoxic activities ($IC_{50}$) were tested on parental and resistant ovarian cancer cell lines. They represent models of conjugates between biologically active vectors and cytotoxic $Pt^{II}$ moieties within the "drug targeting and delivery strategy". Three drugs, routinely employed in the clinical treatment of cancer, namely, cisplatin, carboplatin, and oxaliplatin, were also included in the study as controls. The quantitative structure–activity relationship approach provides simple regression models able to predict $\log(1/IC_{50})$ of diamine–platinum(II) complexes on both parental and resistant ovarian cancer cell lines. The 16 complexes were characterized using 197 molecular descriptors, after which the best regression models relating a subset of these descriptors to the $\log(1/IC_{50})$ in the two cancer cell lines were calculated. Models with four variables proved to be endowed with very good predictive ability $Q^2_{LMO-50\%} \geq 85.6\%$, making it possible to discard 50% of the molecules from the test set following for cross-validation procedure. A four-variable regression model also proved effective in predicting the resistance index RI, $Q^2_{LMO-50\%} = 84.4\%$.

4) QSAR models can be used to make predictions on other platinum-based compounds

- We enstablished an ODE-based qAOP framework.
- We proposed KE mapping methods for several data types.
- We used ODE – based computational modeling to unravel the mechanisms of platinum-induced nephrotoxicity using in vitro RPTEC/TERT1 and in vivo rat kidney data after cisplatin exposure.
- We proposed an alternative QIVIVE-based approach to predict adverse outcomes of other platinum-based compounds.

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