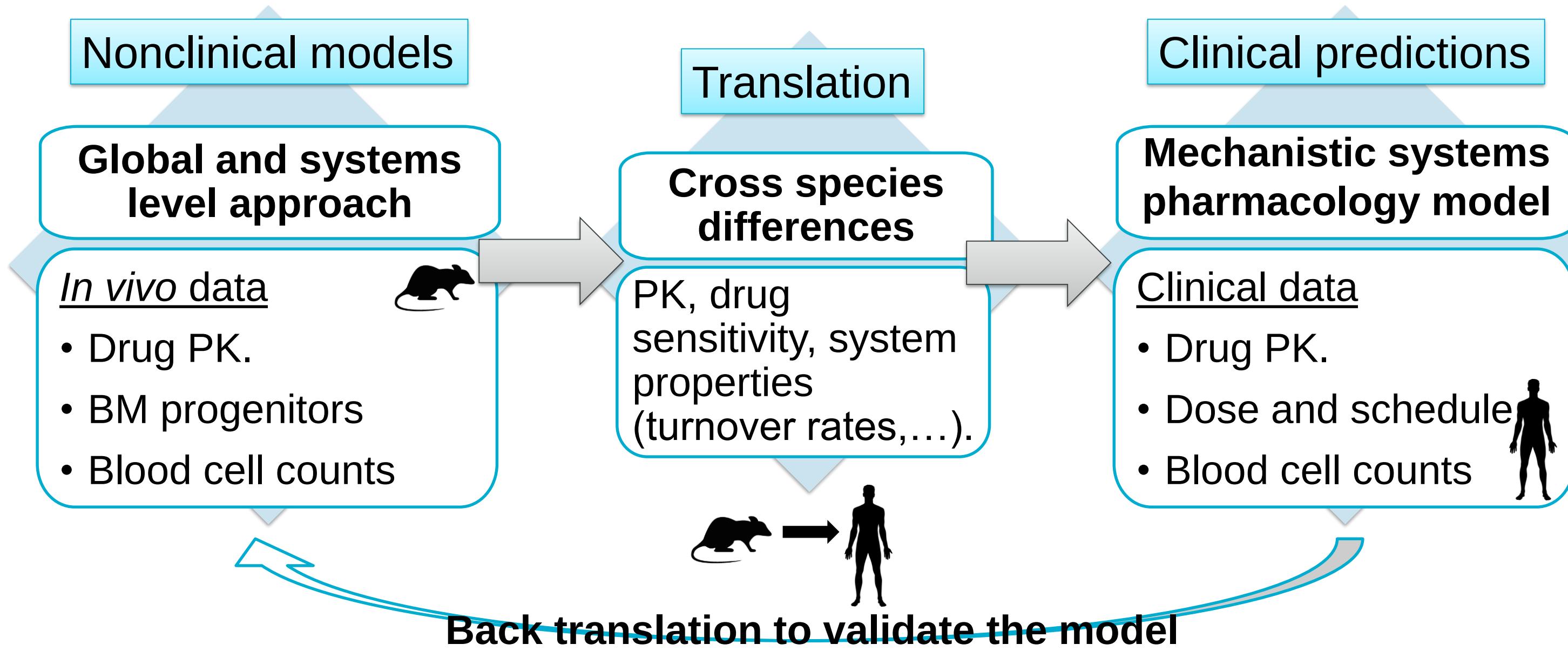


Development of a haematopoiesis model for predictions of carboplatin-induced bone marrow toxicity

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1. Drug-induced bone marrow (BM) toxicity is the most common dose limiting toxicity in oncology



Mathematical modelling is a powerful ally to understanding the mechanisms of drug-induced haematotoxicity (e.g. neutropenia, anaemia, thrombocytopenia, etc.) [1], scaling results from animal models to humans, and designing optimized treatment regimens.

Major problems with existing approaches:

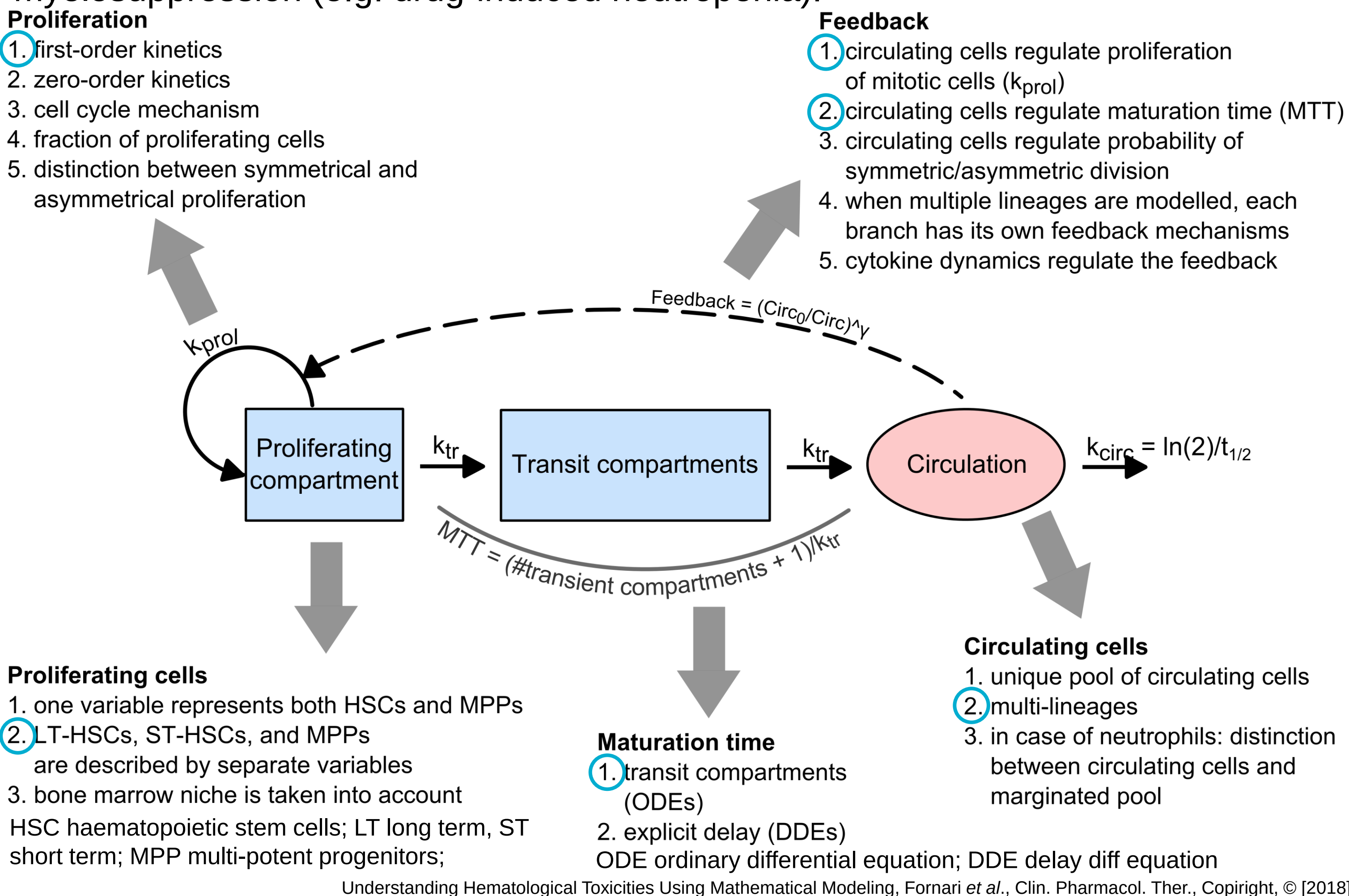
1. effects in the BM are usually inferred from differential blood counts (due to the invasiveness of BM biopsy), and this inference might not be robust;
2. each blood cell type is modelled independently.

Including these features can explain the overall myelosuppression profile induced by oncology drugs, [1].

2. Reference model and mechanistic expansions

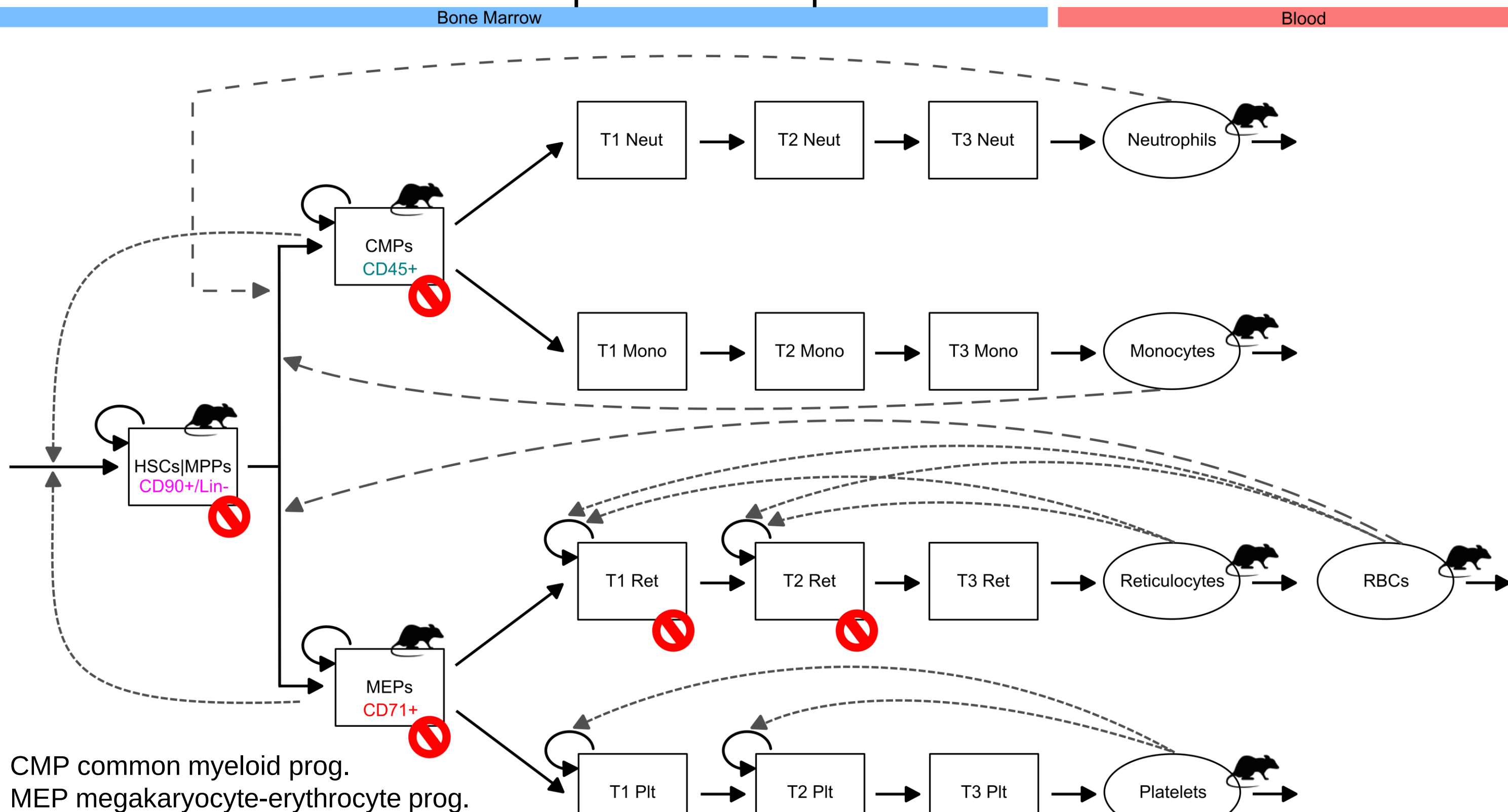
Figure 1 General representation of Friberg model [2], with BM compartments in blue and blood cells in red. Grey arrows point to mechanistic motifs that can be implemented in this framework to expand Friberg model, [1].

Haematopoiesis is depicted as a linear cascade, focussing only on a specific type of myelosuppression (e.g. drug-induced neutropenia).



3. How do carbo-induced variations in progenitor cell populations propagate to all blood cells?

Figure 2 Toxicity in the BM is mechanistically linked with effects in the blood. Effects in rat BM are quantified by FACS analysis, while in the periphery via differential blood counts. Carboplatin affects proliferative cells in the BM.



NOVELTIES

Haematopoiesis is depicted as a tree, instead of as a linear cascade.

Proliferation occurs also in some of Ret. an Plt. transit comp (i.e. T1,T2).

Addition of a effect compartment (PK).

HSCs feed cells into MPPs (source), and this flow is controlled by prog. in the BM, while MPP maturation is controlled by cells in the blood.

MOTIVATIONS

All lineages in the blood derive from a set of common progenitors in the BM.

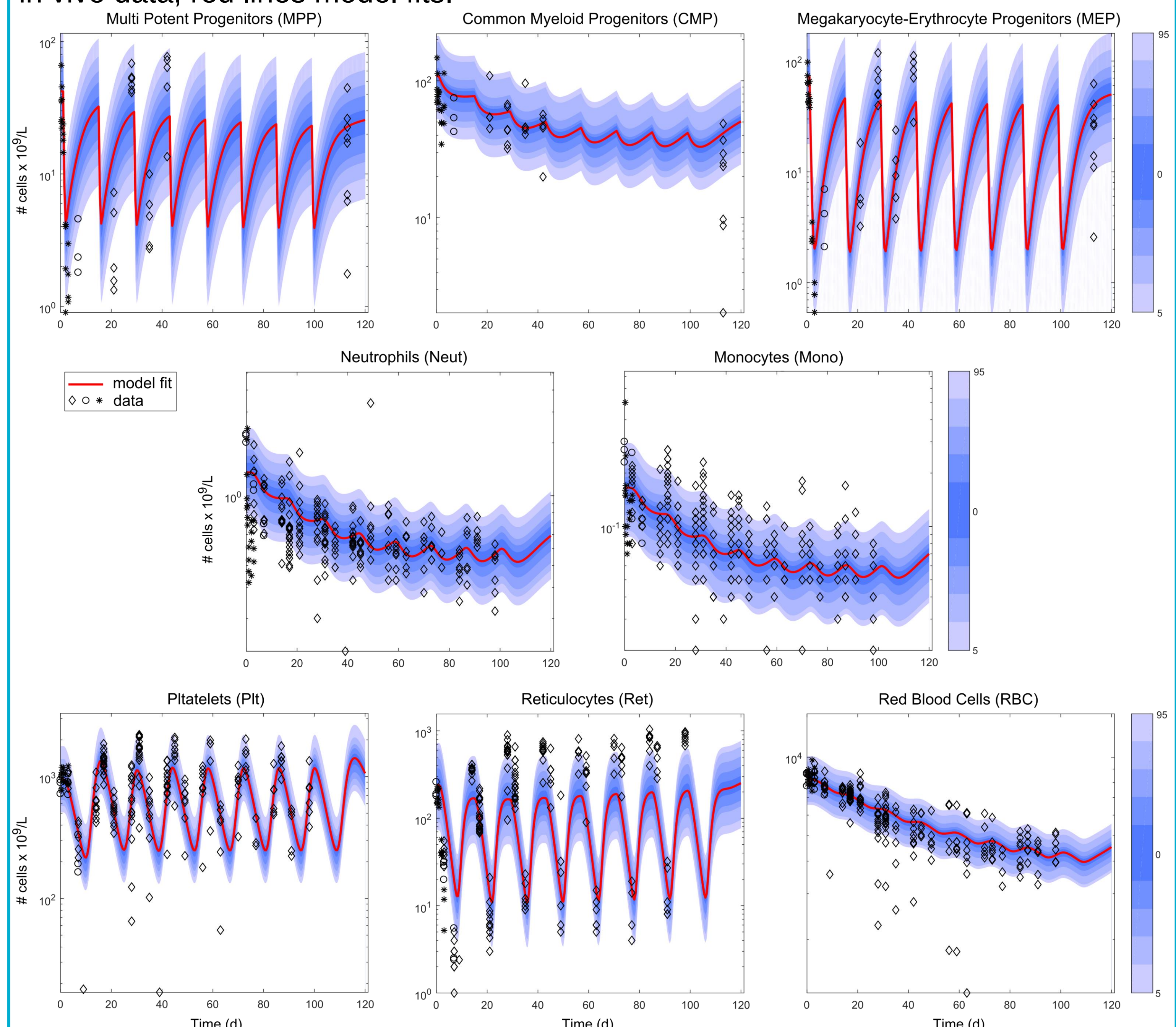
Big oscillations in the periphery could not be explained by MEP proliferation only.

Delay between Cmax time and BM effects

Progenitor fate decision is controlled by multiple inputs coming from the BM and the blood, whose aim is repristinating homeostasis in the whole system.

4. Overall carboplatin-induced myelotoxicity

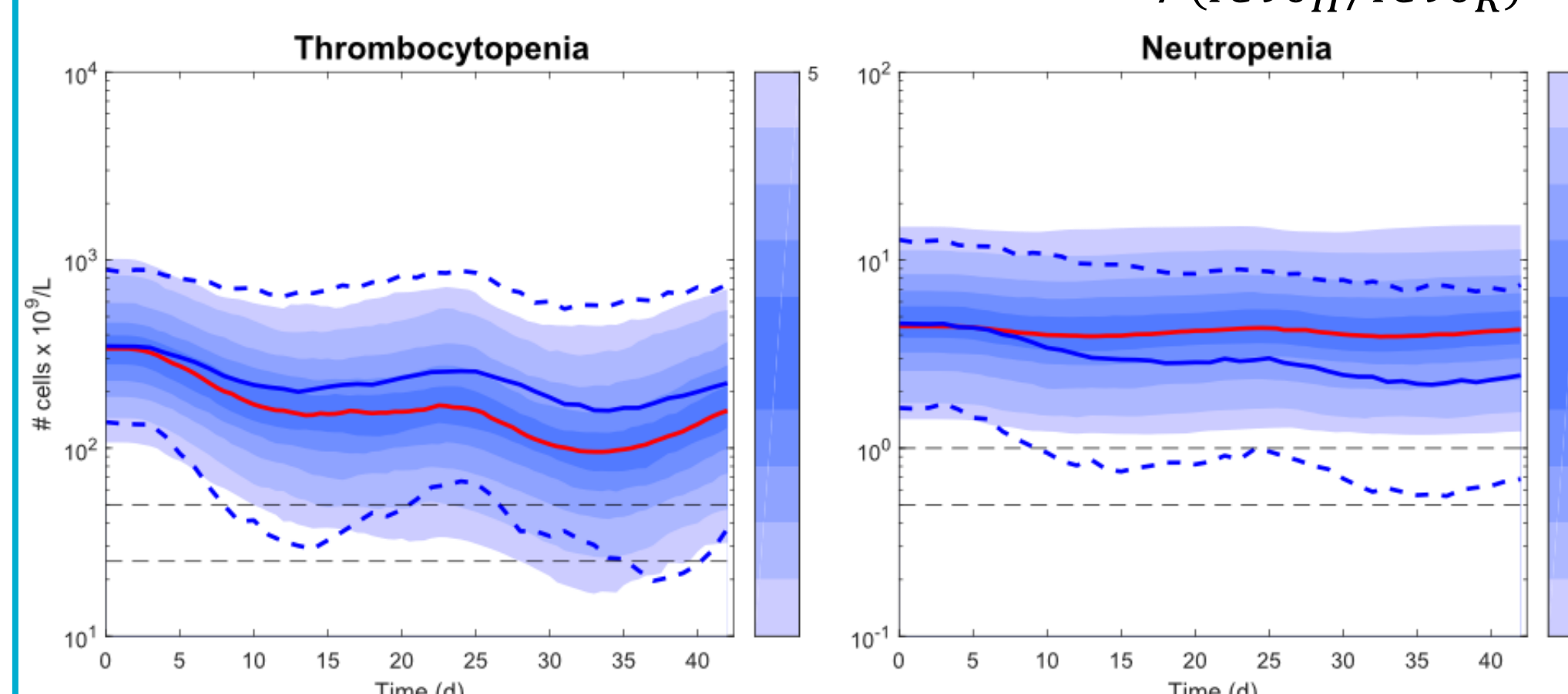
Figure 3 Time courses of carboplatin-induced haematotoxicity in rats. Effects of carboplatin [40 mg/Kg] given every 14 days for 1, 3, and 8 cycles were investigated, from progenitors in the BM to mature cells in the blood. Black dots are in vivo data, red lines model fits.



- Competition between feedback controlling MPP proliferation and maturation makes progenitor counts go down over multiple cycles.
- Proliferation in the transit compartments of Ret and Plt, and the relatively short lifespan of platelets and reticulocytes, explain the big oscillations observed in periphery.

5. Clinical predictions for platelets and neutrophils

Figure 4 Predictions are generated with the rat model, using *human* parameter values. Drug-independent parameters are taken from literature or allometrically scaled from rat values, while drug effects are scaled from rat values using species sensitivity, [3], i.e. $Slope_{Human} = Slope_{Rat} / (IC_{90H}/IC_{90R})$.



Reference clinical data are simulated (solid and dotted blue lines), [4]. Solid red lines are our predictions (median values), while shadow areas show percentiles.

Thrombocytopenia is well predicted using the species sensitivity to scale the slope value estimated from rats, while further work is required to understand why neutropenia is under-predicted using the same scaling.

References

- [1] Fornari *et al.*, CPT, 2018;
- [2] Friberg *et al.*, JCO, 2002;
- [3] Friberg *et al.*, Invest New Drugs, 2010;
- [4] Schmitt *et al.*, JCO, 2010