

Importance of stability analysis when using non-linear semi-mechanistic models to describe drug-induced haematotoxicity

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1. Background

Stability analysis is an essential tool to understand systems' behaviour [1, 2].

To our knowledge, the stability properties of the semi-mechanistic model developed by Friberg *et al.* [3] to investigate drug-induced haematotoxicity, have not been assessed before.

Here we use stability analysis techniques to gain new insights into the relationship between parameters and system behaviours.

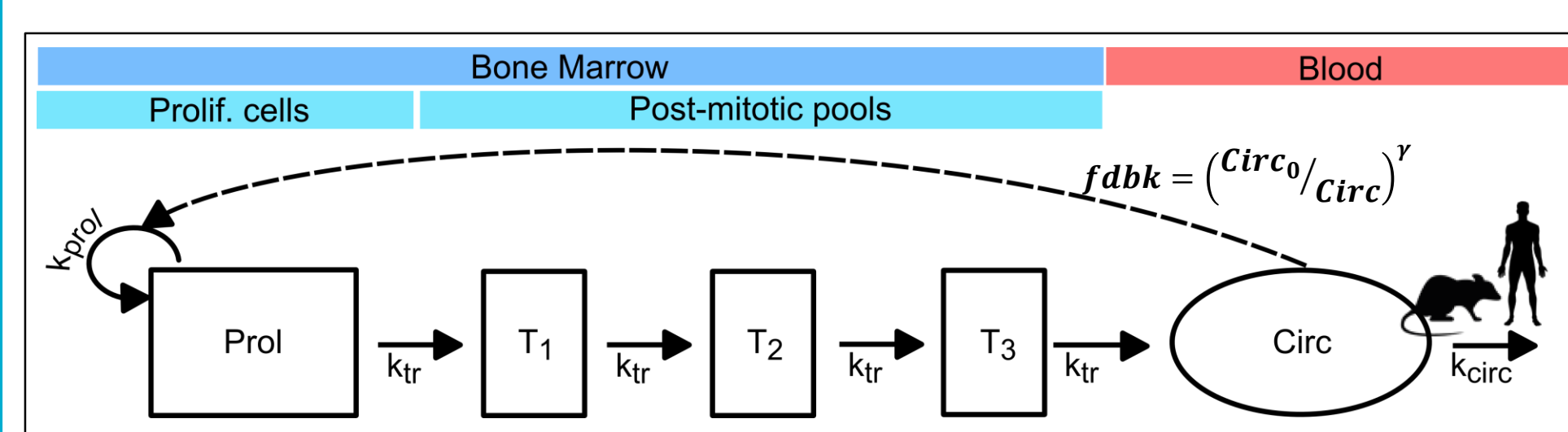
We discuss these results in the context of non-linear mixed effects modelling, highlighting the consequences in prediction performance, and providing recommendations for future analysis.

2. Method

The stability analysis of the semi-mechanistic model developed by Friberg *et al.* [3], and of some of its variations, was performed linearizing the system of non-linear differential equations around the steady state of interest (namely the homeostatic values, X^*), and then characterizing the long-term behaviour of the linearized system in the neighbourhood of this steady state (X^*), [2]. The Routh-Hurwitz criteria [2] were used to investigate the nature of the steady state X^* , and Routh-Hurwitz conditions were solved in Mathematica (Wolfram Research, Inc, ver 11.0).

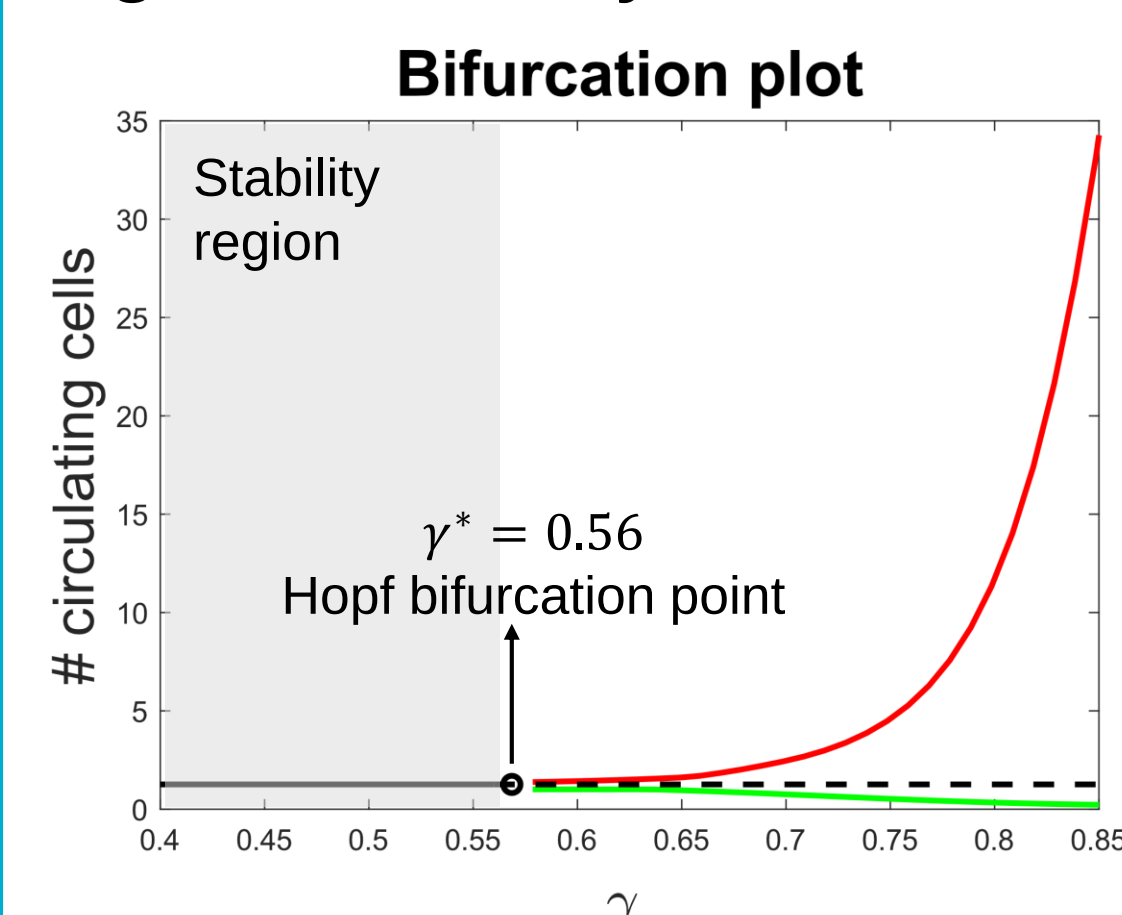
3. Stability analysis of Friberg model [3]

Effects of oncology drugs on haematopoiesis are described with a transit-compartment model, which comprises proliferation in the bone marrow, cell maturation and release of mature cells into the blood [3].



- 3 parameters $Circ_0, \gamma, k_{circ}$
- End points: blood cell counts

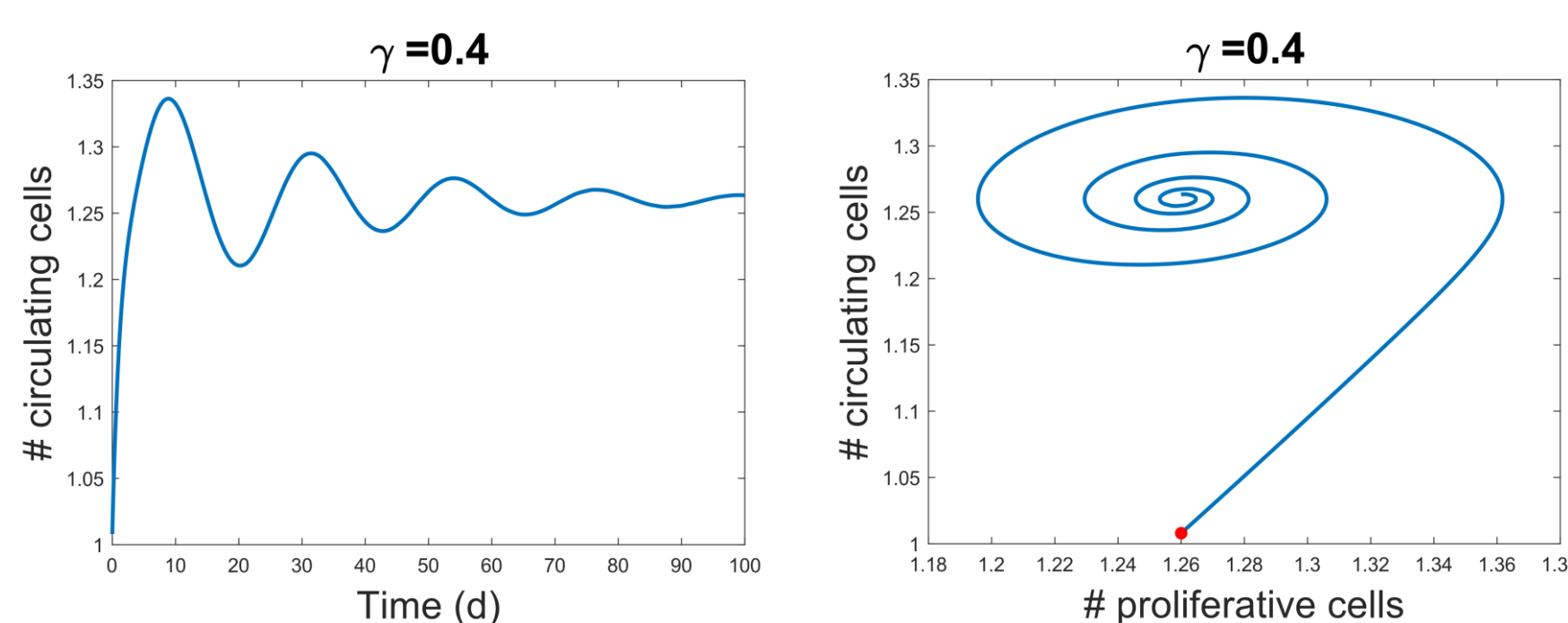
Alteration in blood counts activate the feedback loop, and model solutions return to homeostasis only if parameters are in the stability region of the system.



On crossing the bifurcation point γ^* , the steady state (solid black line) becomes unstable (dotted black line), and a periodic limit cycle solution appears (red and green lines show the maximum and the minimum of the oscillations, respectively).

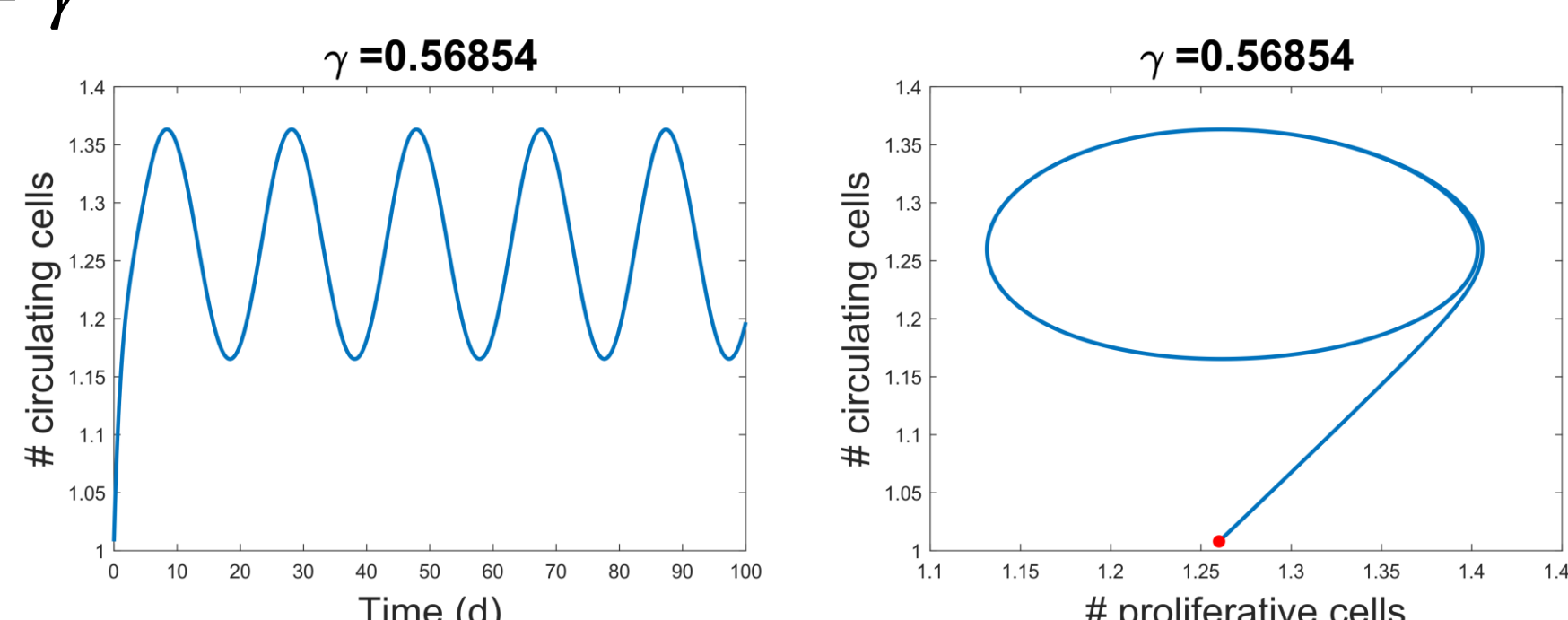
Stable steady state: $\gamma < \gamma^*$

- Decaying oscillations.
- Physiological response of haematopoiesis to drug-induced perturbations.



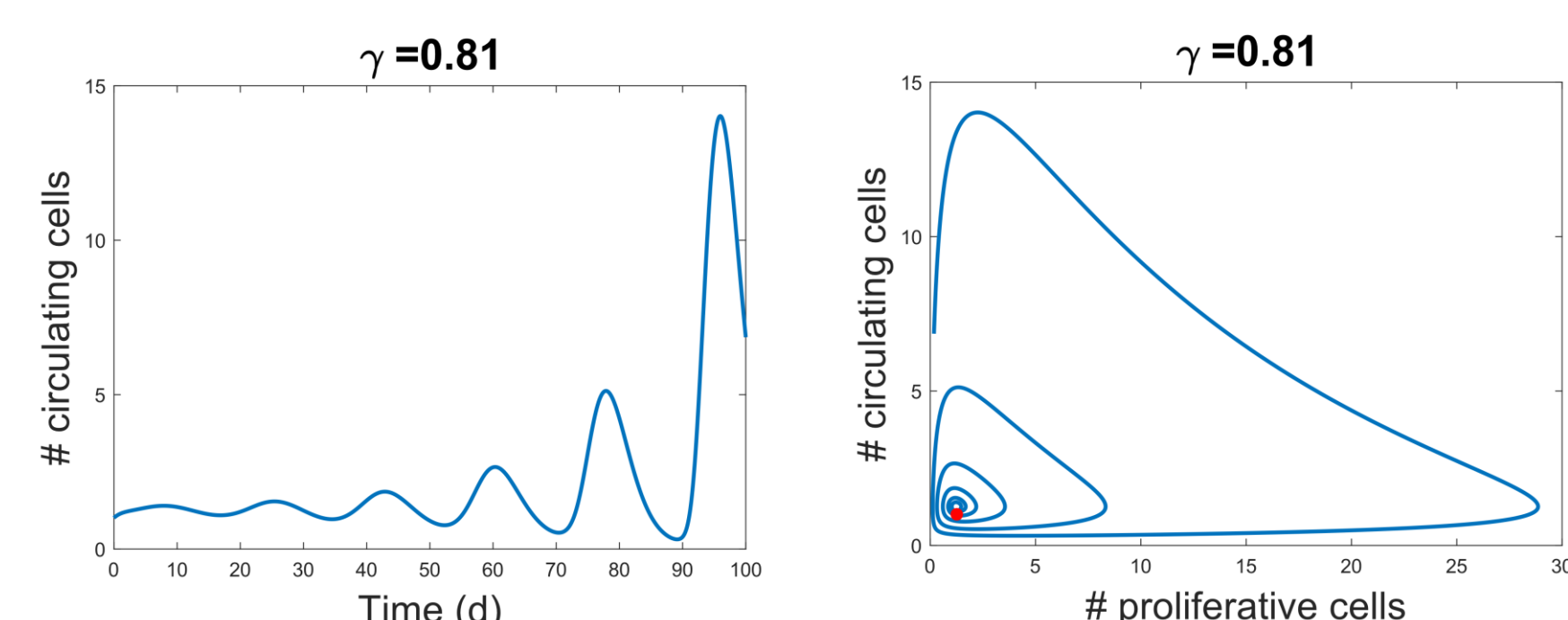
Stable periodic limit cycle: $\gamma = \gamma^*$

- Periodic oscillations
- Periodic haematological diseases (e.g. cyclical neutropenia).



Unstable steady state: $\gamma > \gamma^*$

- Growing oscillation
- Non-physiological response of haematopoiesis to perturbations.

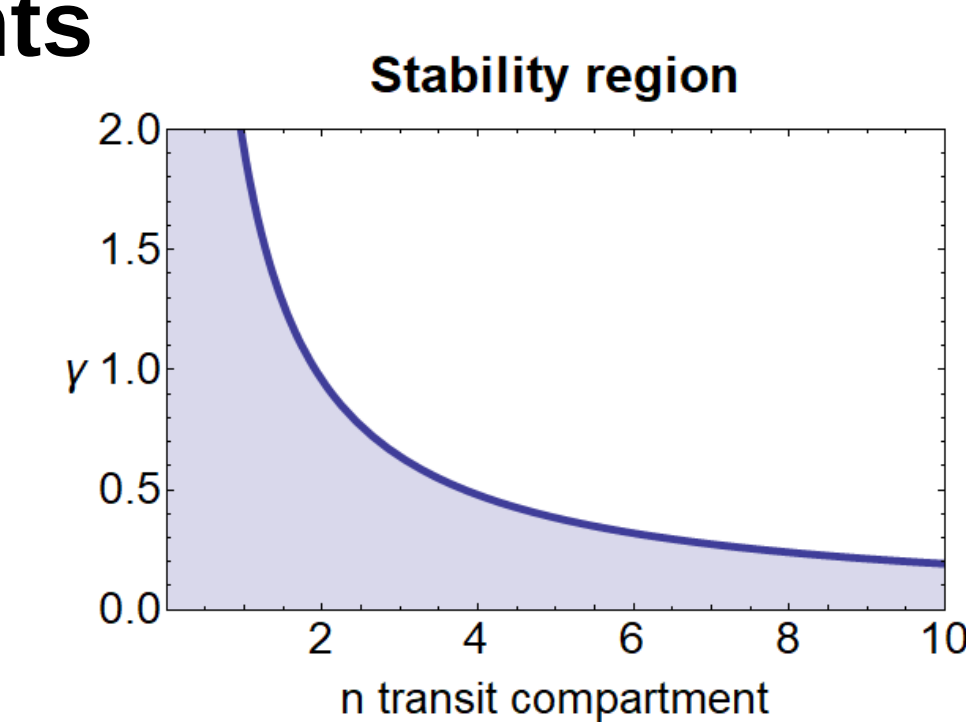
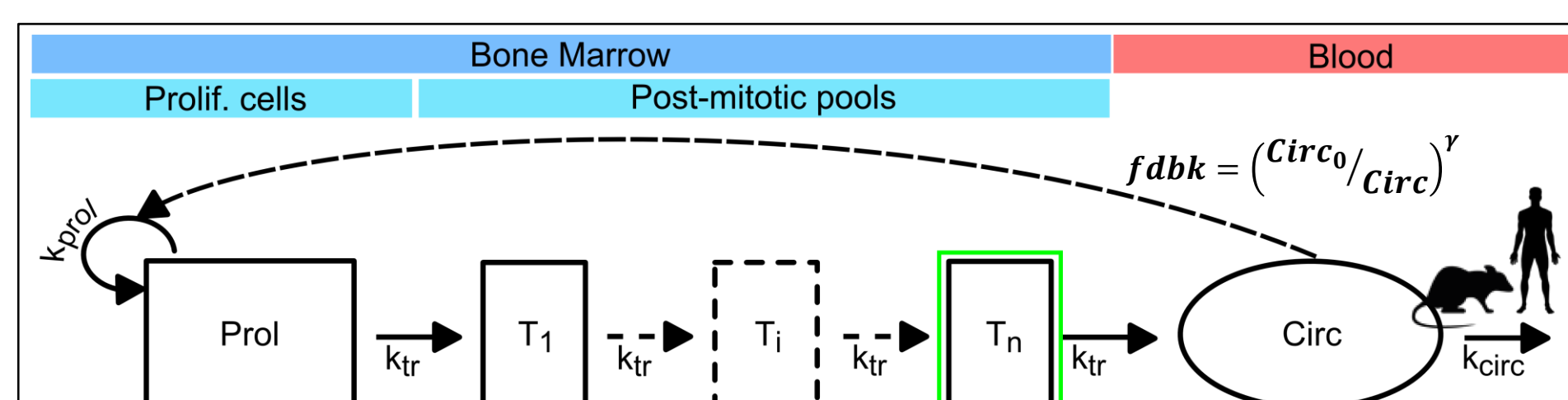


4. Stability & MTT, number and size of compartments

The stability analysis of Friberg model ($\gamma < \gamma^*$) derives from the model structure itself, and it is independent of the other parameter values, and of the type of toxicity or perturbation.

Therefore, if we alter the model structure (e.g. number of transit compartments, or the size of the proliferative cells) the following new stability conditions hold.

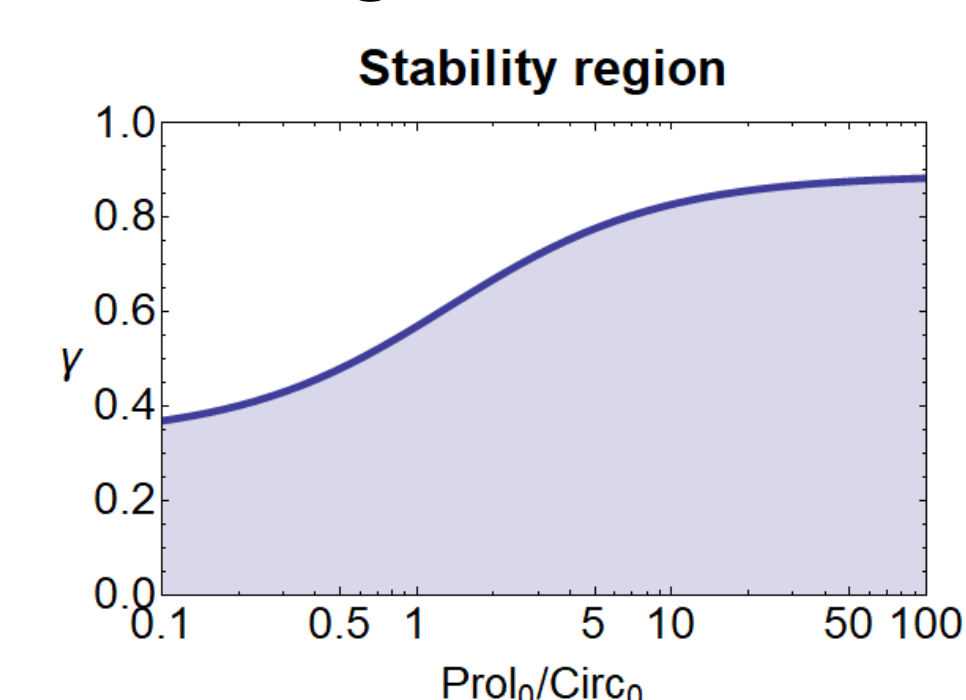
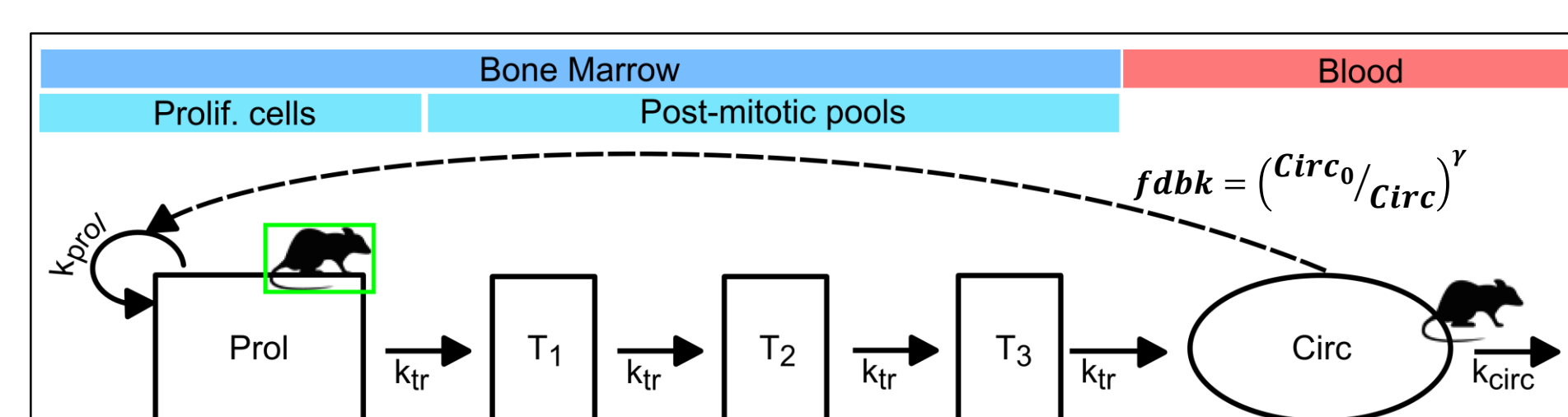
A) Varying the number of transit compartments



3 parameters: $Circ_0, \gamma, k_{circ}$
n maturation compartments: variable
End points: blood cell counts

Stability region
 $\gamma \leq f(n) = 1.9/n$

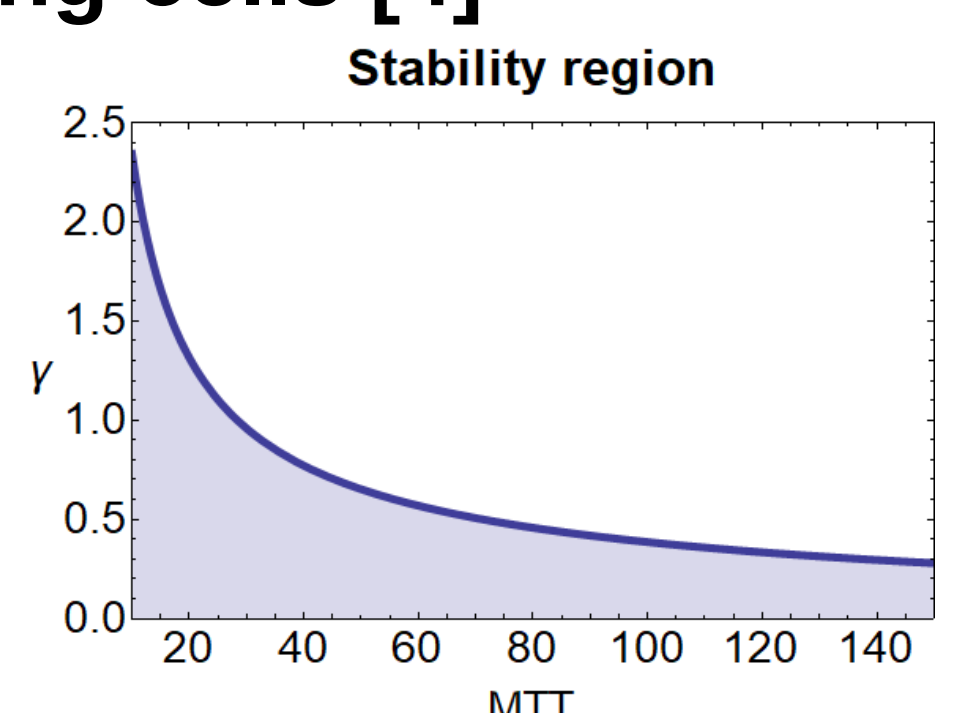
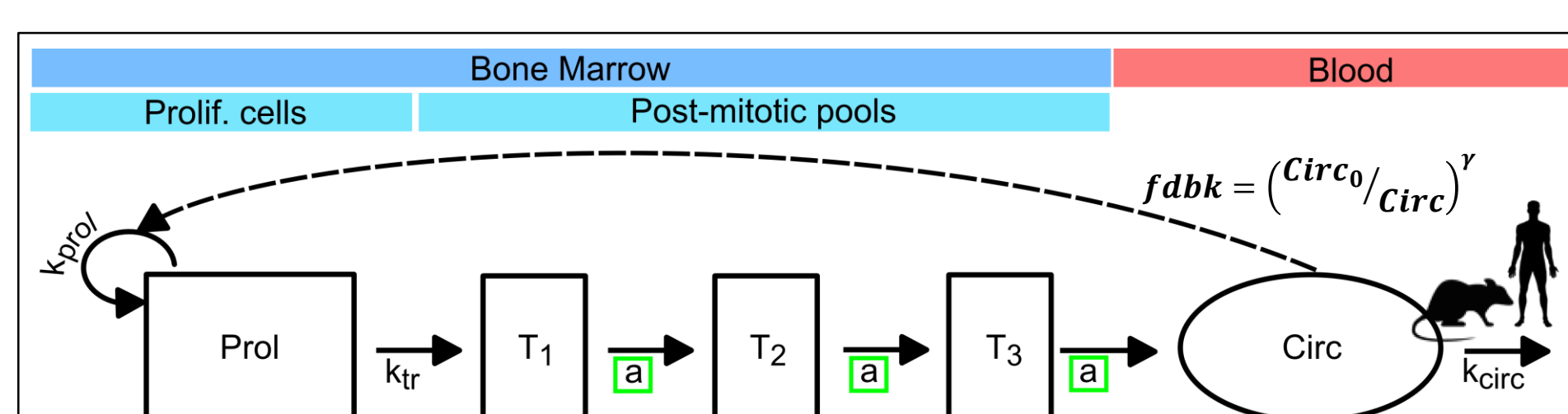
B) Size of proliferative compartment $\neq$ size circulating cells



4 parameters: $Circ_0, \gamma, k_{circ}, Prol_0$
n maturation compartments: 3
End points: blood cell counts, BM progenitors

Stability region
 $\gamma \leq f(Prol_0/Circ_0)$

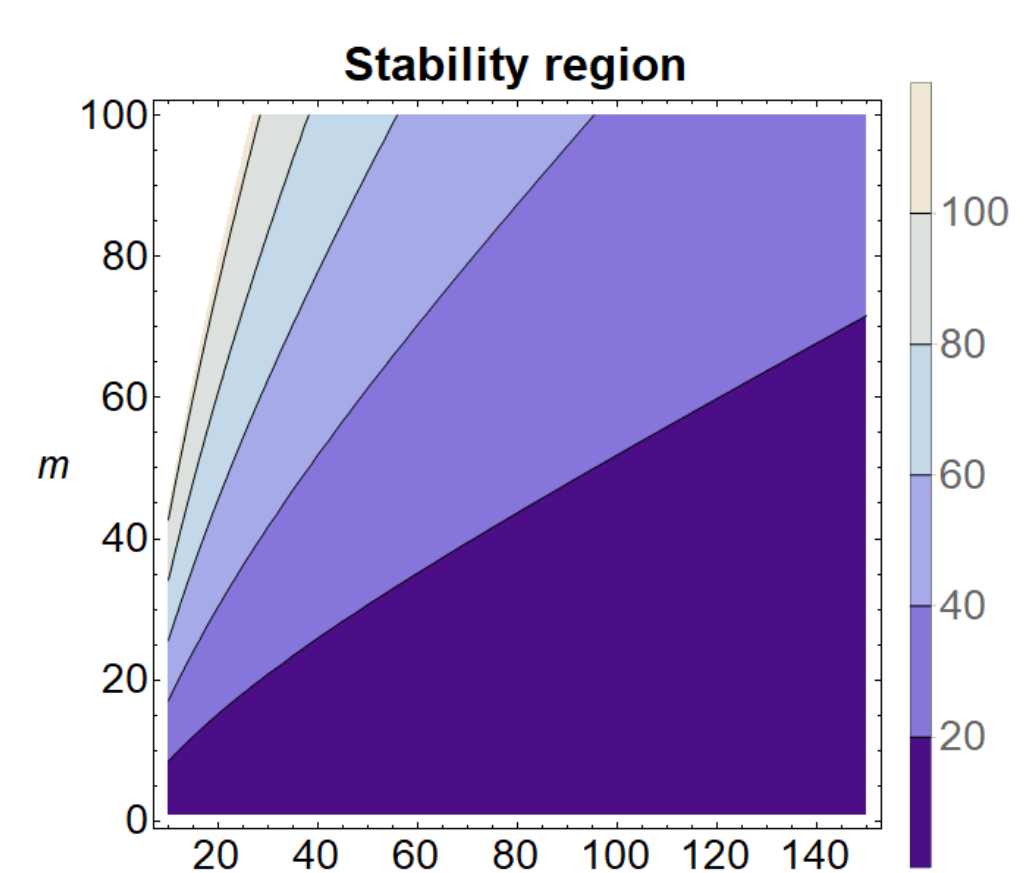
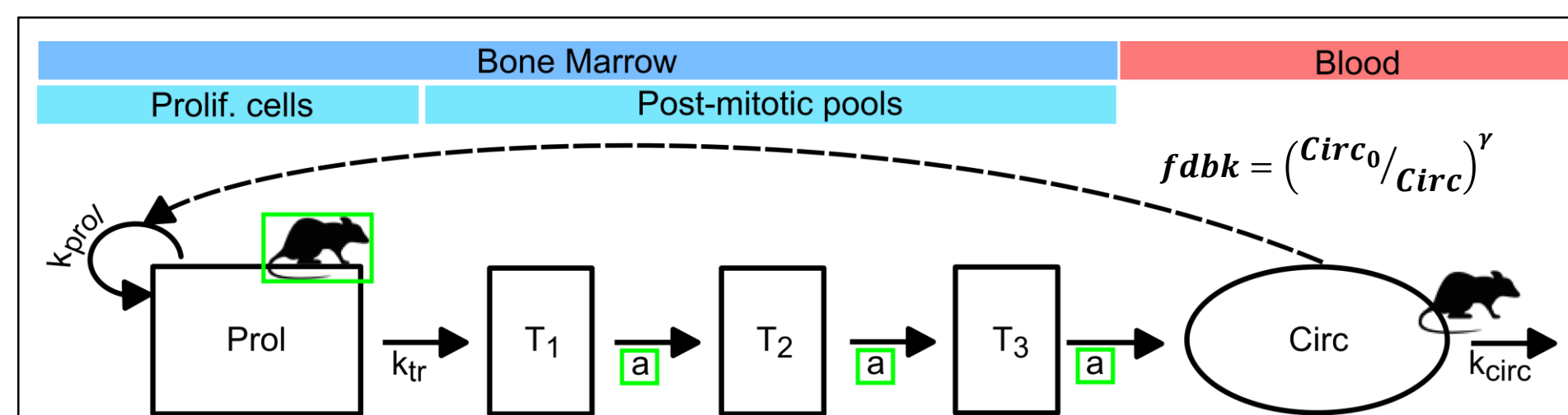
C) Maturation rate $\neq$ elimination rate circulating cells [4]



4 parameters: $Circ_0, \gamma, a$
n maturation compartments: 3
End points: blood cell counts

Stability region
 $\gamma \leq f(MTT = 3/a)$

D) Hypotheses B and C together



4 parameters: $Circ_0, \gamma, a, Prol_0$
n maturation compartments: 3
End points: blood cell counts, BM progenitors

$\gamma \leq f(Prol_0/Circ_0, 3/a)$

5. Discussions

The behaviour of a model is a consequence of its structure and network topology [1]. Therefore, we highly recommend to incorporate the result of this study

$$\gamma \leq \gamma^* = f(par)$$

when applying Friberg model [3], of some of its variations, to describe drug-induced haematotoxicity. For instance, we suggest to use a logistic transformation to constrain individual gamma estimates to the stable region, for mixed effects parameterisations. This will guarantee mathematical stability and, thus, avoid a non-physiological behaviour of the system.

6. References

- [1] Bakshi *et al.*, CPT:PSP, 2016; [3] Friberg *et al.*, JCO, 2002;
 [2] Murray MathBio I, Springer, 2002; [4] CâmaraDeSouza *et al.*, JPKPD, 2018