Modelling the Dynamics of Hematopoietic Stem Cells

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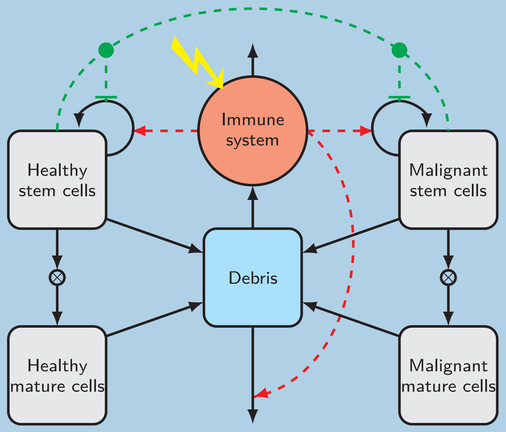
Motivation and background

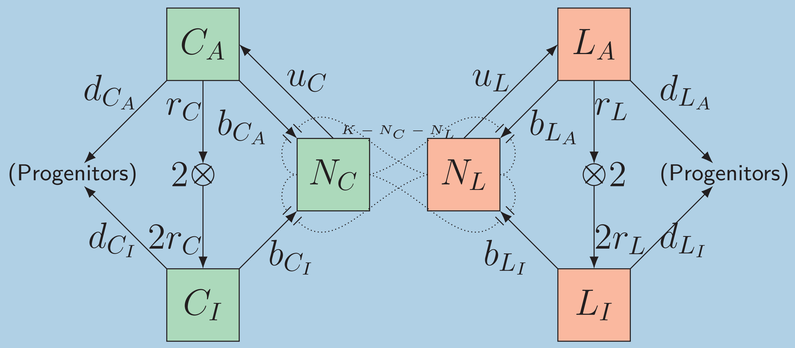


Andersen et al (2017) present a mechanism-based mathematical model describing the hematopoietic (blood-producing) system of the human body during the development of the Myeloproliferative Neoplasms (MPNs), a group of slowly developing blood cancers.
The model consists of a six-dimensional system of ODEs.
Through time-scale considerations, the model can be reduced to a simpler two-dimensional system describing the slow dynamics (Ottesen et al, 2019).
So far, model analysis has granted some insight about the cytokines related to MPNs as well as prediction of patient-specific treatment response.

However, some changes to the model are currently being considered:

- A subset of patients display response that are not readily reproducible by the present model formulation.
- The treatment considered (INF-α) is known to affect features of the hematopoietic system not currently included in the model.

Mechanisms of stem cells



N: Niche-bound; A: Free, active; I: Free, inactive. C and L denote cell-types.

- The figure depicts a compartment diagram of a separate model considering solely the hematopoietic stem cells within the bone marrow micro-environment.
- Inspired by the work of Wang et al (2017), the model considers competition between stem cells in a finite stem cell niche of capacity K.
- Stem cells bound to the niche are considered quiescent while free stem cells can divide, differentiate or return to quiescence by rebinding with the niche.

Results

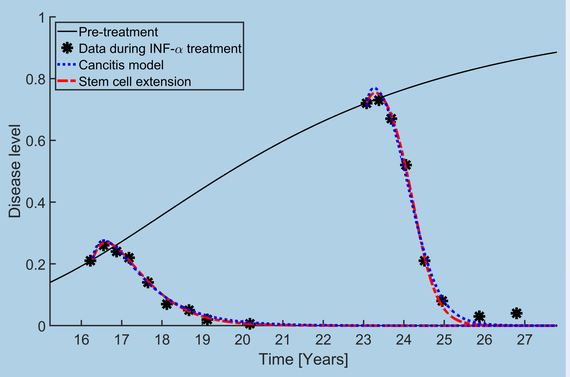
- Time-scale considerations allow for a reduction of the stem cell model to a system of two ODEs, modelling the slow time-scale.

$$\dot{N}_C = \left(\frac{2(1-N_C-N_L)}{\alpha_C+1-N_C-N_L}\left(\frac{r_C}{r_C+d_{C_A}}\right)-1\right)N_C$$

$$\dot{N}_L = \mu\left(\frac{2(1-N_C-N_L)}{\alpha_L+1-N_C-N_L}\left(\frac{r_L}{r_L+d_{L_A}}\right)-1\right)N_L$$

Where $\alpha_C = d_{C_I}/(b_{C_I}K)$, $\alpha_L = d_{L_I}/(b_{C_I}K)$ and $\mu = u_L/u_C$

- Stem cell compartments in the Cancitis model can be replaced with the slow time-scale stem cell model leading to an extended model.
- The figure displays disease development, two examples of data for patients undergoing treatment as well as simulate treatment in the models.
- Both the normal and extended model can reproduce the responses to treatment, by step-wise changing parameters at treatment onset.



Preliminary conclusions

- When modelling treatment-response of MPN patients, the Cancitis model implies **increased elimination** of malignant cells as response to treatment.
- The model can be extended to include the **stem cell dynamics** more accurately, which allows for **alternative hypotheses about which parameters are affected by treatment**.
- Preliminary results suggests that **increased activation of quiescent stem cells** ($u_C \uparrow$ and $u_L \uparrow$) and increased differentiation ($d_{L_I} \uparrow$) lead to the delayed responses seen in data.

References

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