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Combining two model paradigms: How an agent-based hematopoietic stem cell model couples to an ordinary differential equations model of mature granulopoiesis and chemotherapy

To model the organization of hematopoietic stem cells Roeder *et al.* have introduced an agent-based model which succeeded well in explaining several experimental data of clonal competition and stem cell dynamics with clinically relevant applications in the field of chronic myeloid leukemia [1]. The model assumes two growth-environments and regulates stem cell activity by an intrinsic feedback that controls the transition between these environments.

In order to model the effects of chemotherapy and growth factor applications on the number of mature granulocytes, a compartment-based ordinary differential equations (ODE) model of granulopoiesis has been introduced by Scholz *et al.* [2]. Here the stem cell compartment is represented in a very simplified fashion.

To overcome this simplification and to take advantage of the established model of hematopoietic stem cells we replaced the ODE stem cell compartment with a difference equation formulation of the agent-based stem cell model [3]. Two feedback mechanisms for stem cell activation were introduced for replacing the regulation of self-renewal probability and proliferative fraction in the stem cell compartments of the ODE model. Stem cell activation was implemented firstly by increasing the probability of exiting quiescent states and secondly by a general acceleration in the stem cell compartment.

The resulting hybrid model was capable of reproducing the experimental data for the chemotherapy regime of Chop21. Interestingly, the comparison of feedback mechanisms for stem cell activation showed that the best agreement with the regeneration response in the clinical trials was achieved for the intrinsic regulation of the agent-based model without additional activation.

On the basis of the combined model, we aim to improve the modeling of chemotherapy effects on the hematopoietic system in the future. In particular we expect further insights into the role of role of hematopoietic stem cells with respect to the development of a toxicity induced leukopoenia with subsequent regeneration

References

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