Towards New Clinical Hypotheses using a Mathematical Model of Acute Leukemias

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Abstract

Background: Mathematical modelling can give valuable insights into the characteristic behavior of biological systems. In the research of acute leukemias a growing body of literature describes modelling approaches to explain the mechanistics of hematopoietic cells with respect to the emergence of leukemic diseases.
Methods: We analyzed a mathematical model, based on ordinary differential equations, published by Stiehl et al. (J.R.S. Interface, 2014), to characterize acute leukemias. In the model we primarily focused on the dependence of the duration from the first mutation to the diagnosis of the leukemic disease (time-to-diagnosis) on leukemic stem cell's (LSC) selfrenewal and proliferation rates. We simulated a healthy hematopoietic system and added a small amount of mutated stem cells with predefined proliferation (range: 0-2) and selfrenewal (range: 0-1) to the system. The development of a leukemia is observed for 2000 days and the time-to-diagnosis (days) is calculated for each parameter combination.
Results: The model shows that even slowly proliferating LSC can become a leukemia when selfrenewal is high enough. The analysis of the time-to-diagnosis showed that LSC with high proliferation and high selfrenewal are responsible for "fast" leukemias, i.e., lead to a short time between initial mutation and diagnosis, while decreased proliferation or decreased selfrenewal leads to "slower" leukemias.

Methods

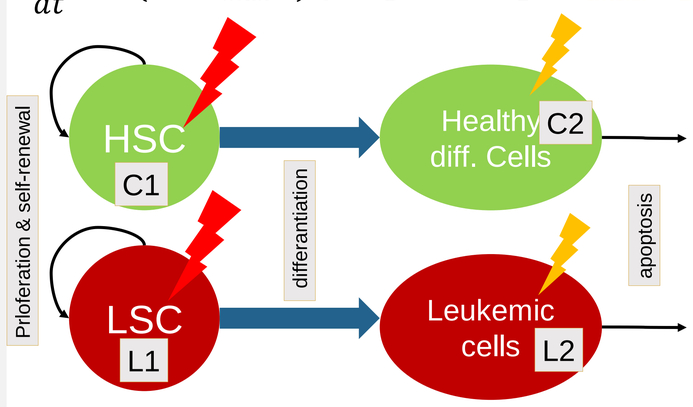
A mathematical model of acute leukemias,published by Stiehl et al. [1] was adapted and tested for its behaviour regarding a leukemias pace and the effect of treatment. The model represents a population marginal model on the leukemic clones, i.e. only one clone is modelled representing the averaged properties of a mixture of clones.

$$\frac{dC_1}{dt} = (2a^c_{max}\, s - 1)\, p^c\ C_1 - d^x_t\ C_1 - k_{chemo}\ p^c\ C_1$$

$$\frac{dC_2}{dt} = 2(1 - a^c_{max}\, s)\ p^c\ C_1 - d^c\ C_2 - k_{anthr}\ C_2$$

$$\frac{dL_1}{dt} = (2a^l_{max}\, s - 1)\, p^l\ L_1 - d^x_t\ L_1 - k_{chemo}\ p^l\ L_1$$

$$\frac{dL_2}{dt} = 2(1 - a^l_{max}\, s)\ p^l\ L_1 - d^l\ L_2 - k_{anthr}\ L_2$$

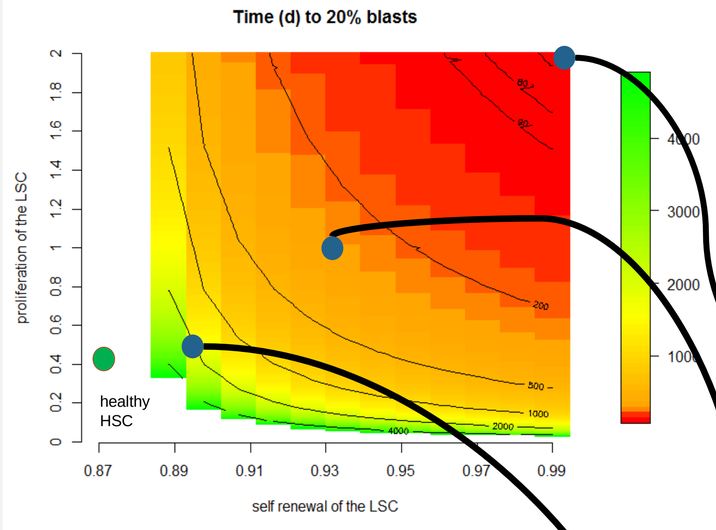


C1(0)	C2(0)	L1(0)	L2(0)
$2 * 10^9\ \frac{cells}{kg}$	$1\ \frac{cells}{kg}$	$1\ \frac{cell}{kg}$	$0\ \frac{cell}{kg}$

p^c	a^c_{max}	d^c	p^l	a^l_{max}	d^l
0.45	0.87	2.3	*varies*	*varies*	0.1

Software note:
Simulations were performed in the statistical software R[2] using packages deSolve [3] and ggplot2 [4].

„Leukemic pace“



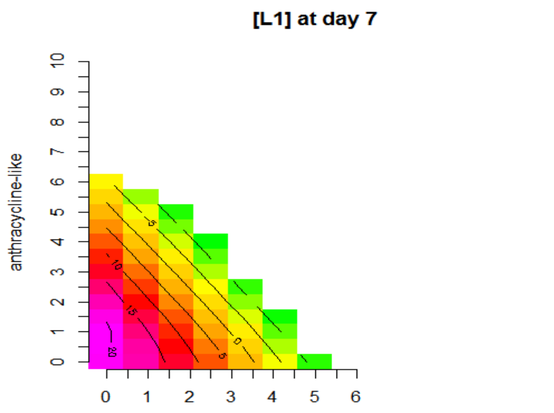
Therapy: „7+3“

Diagnosis

Cytarabine-like
7 days

Anthracycline-like
3 days

Specific therapy intensities for each cytostatic
Anthracycline-like chemotherapy is modelled to act also on differentiated cells, as additional „apoptosis“ rate



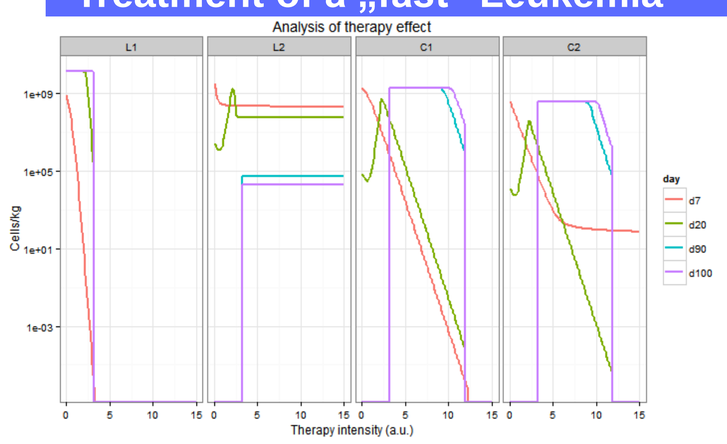
Therapy: 7 days induction therapy

Diagnosis

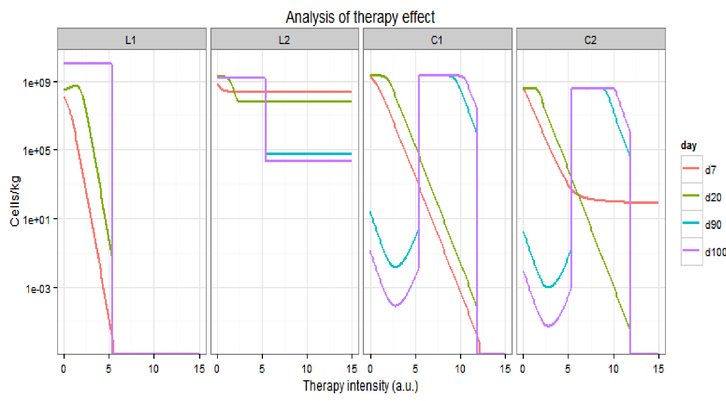
Cytarabine-like
7 days

Therapy effect on mitotic cells is proportional to a cell's proliferation rate

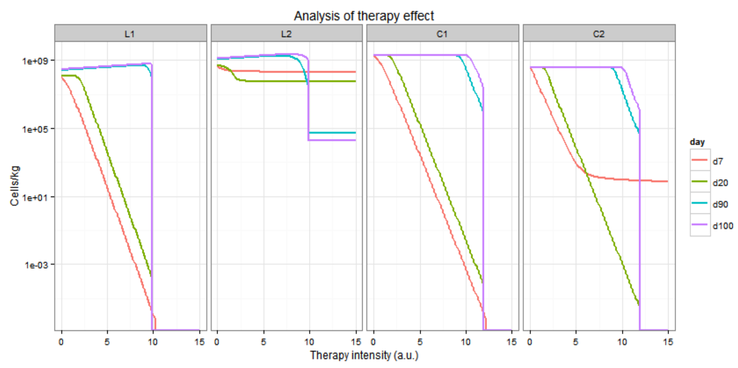
Treatment of a „fast“ Leukemia



Treatment of a „medium“ Leukemia



Treatment of a „slow“ Leukemia



Conclusions & Limitation

- **Also coarse-grained models allow to make predictions about therapy**
- **Different types of therapy can be modelled and assessed**
- **Therapy success also depends on leukemic pace, e.g. determined by genetic factors.**
- **Determination of treatment dosis (e.g. in mg/m²) can not be made easily**
- **Model is calibrated for an „average“ adult, so predictions for other cohorts need adapted models**

References

[1] Thomas Stiehl , Natalia Baran , Anthony D. Ho , Anna Marciniak-Czochra (2014) Clonal selection and therapy resistance in acute leukaemias: mathematical modelling explains different proliferation patterns at diagnosis and relapse. J.R.S. Interface 11: 20140079

[2] (R Development Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.

[3] Karline Soetaert, Thomas Petzoldt, R. Woodrow Setzer (2010). Solving Differential Equations in R: Package deSolve Journal of Statistical Software, 33(9), 1--25.

[4] H. Wickham. ggplot2: elegant graphics for data analysis. Springer New York, 2009.

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No conflict of interest.