A mathematical approach to find effective immunotherapy strategies

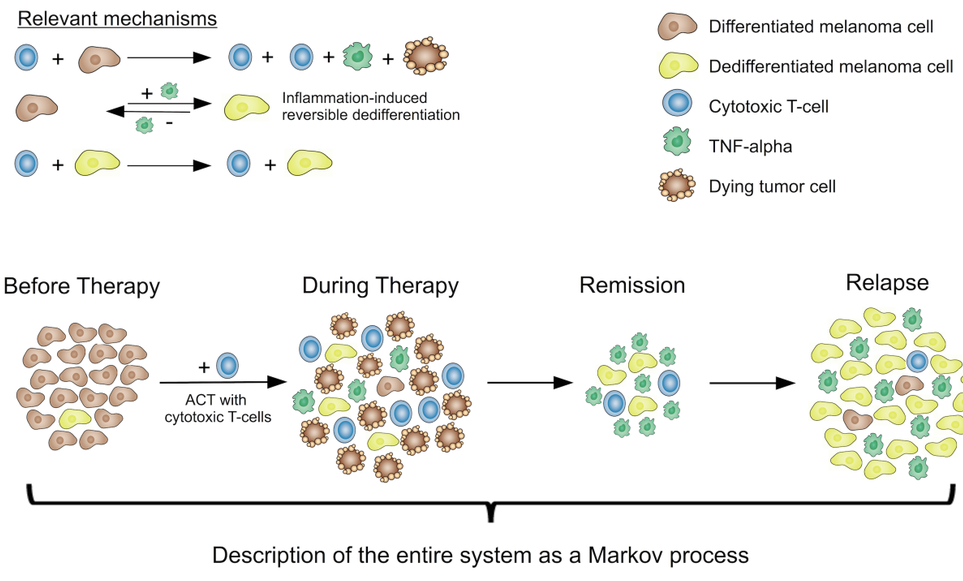
Mayer H.[1,4], **Baar M.**[1,4], **Coquille L.**[1,4], **Hölzel M.**[2], **Neukirch R.**[1], **Prochnau B.**[1], **Rogava M.**[3], **Tüting T.**[3], **Bovier A.**[1]

[1] Institute for Applied Mathematics, University of Bonn, Germany
[2] Institute for Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn, University of Bonn, Germany
[3] Laboratory of Experimental Dermatology, Department of Dermatology and Allergy, University Hospital Bonn, University of Bonn, Germany [4] Equal contribution

Inflammation-induced switch leads to resistance

Landsberg et al. investigate in [5] metastatic melanomas treated with adoptive cell transfer therapies (ACT) with cytotoxic T-cells and observe that

- After a time of remission often a relapse occurs
- Melanoma cells of a different phenotype are present in the relapse
  → change of phenotype is caused by an inflammation-induced, TNF-α mediated downregulation of melanocytic antigens
- This switch enables the melanoma to escape the therapy since they cannot be killed by the T-cells specific for the melanocytic antigen anymore
- Surprisingly, the phenotypic switch is reversible and the loss of the antigen is not permanent
- Proliferation is not required to observe a phenotypic switch
- Depending on the microenvironment the tumor changes the distribution of differentiated melanoma cells bearing the specific antigen and dedifferentiated melonoma cells lacking the melanocytic antigen
- It is suggested that future ACT protocols should target melanocytic and non-melanocytic antigens simultaneously



A mathematical model for melanoma under T-cell therapy

Standard stochastic individual-based models take into account birth and death (due to age or competition) events and mutations, see e.g. [1], [2] or [3].

In order to model the dynamics of a tumor under treatment we extended these models by including **phenotypic switches** and **birth and death events depending on other subpopulations**.

Each individual carries certain clocks: if a clock rings, the next evolution step (dividing, dying, cytokine production, switching, mutation) occurs.

These clocks represent **random** times: For one type of cells the clocks have the same distribution, i.e. the expected time until the next event is for all cells of one type the same but the realizations are random and different for the individual cells.

More precisely, we distinguished three types of subpopulations: Melanoma cells, T-cells and cytokines. They carry the following clocks:

1. Each **melanoma cell** has several independent exponential clocks
   (with parameters which are different for the differentiated and the dedifferentiated phenotype):
   - a *cell division clock*, a *natural death clock*, a *competition death clock* depending on the number of differentiated and dedifferentiated melanoma cells and
   - a ***natural switch*** *clock*

   Differentiated melanoma cells have in addition
   - an ***inflammation induced switch*** *clock* depending on the amount of TNF-α present in the system.
2. Each **cytotoxic T-cell** has three independent exponential clocks:
   - a *natural death clock* and
   - a ***cell division clock*** depending on the number of melanoma cells they can kill (TNF-α is secreted at these birth events)
   - a ***killing clock*** depending on the number of melanoma cells they can kill (TNF-α is secreted at these killing events)
3. Each **TNF-α** protein has one exponential clock:
   - a *natural death clock*

   Remark: A fixed amount of TNF-α is produced when T-cells are produced and when melanoma cells are killed at random times

Simulations: Therapy with T-cells of one specificity

In certain setups the probability that the effective T-cells die out is positive. This leads to different realizations of the (random) system due to fluctuations:

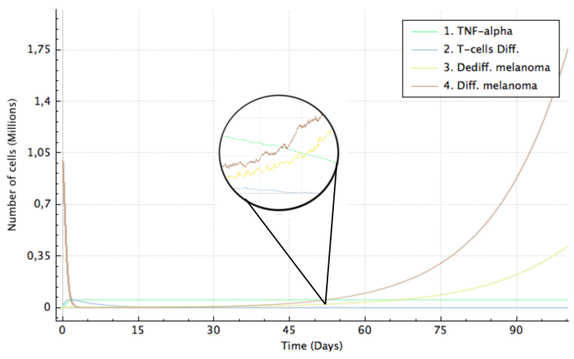


Figure 1: T-cells die out

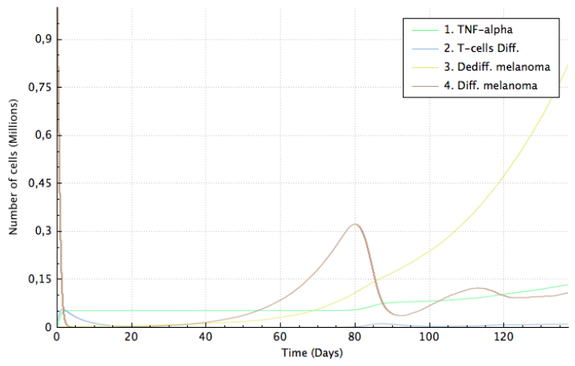


Figure 2: T-cells survive

In Figure 1 the T-cells died out and a relapse appears. Due to the presence of TNF-α the relapse is a mixture of differentiated and dedifferentiated melanoma cells. In contrast, in Figure 2 T-cells survive at a very low level and are activated when the number of differentiated melanoma cells increases again. The relapse consists mainly of the dedifferentiated phenotype.

This different behaviors cannot be covered when the dynamics of T-cells and TNF-α are modeled with deterministic functions. The **random fluctuations** are important.

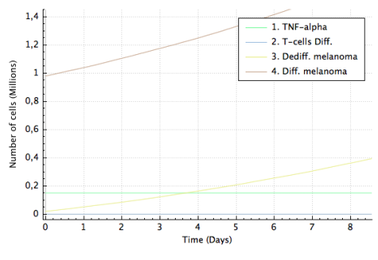


Figure 3: Low TNF-α

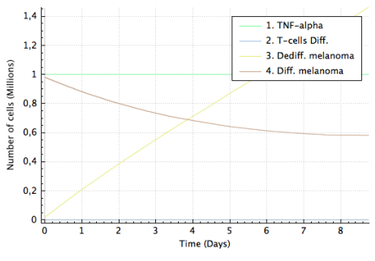


Figure 4: High TNF-α

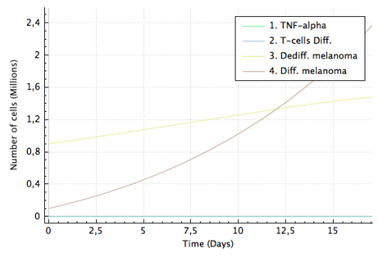


Figure 5: No TNF-α

Presence of TNF-α induces the switch to an equilibrium with a high concentration of the dedifferentiated phenotype. Higher concentration of TNF-α accelerates switching. Without TNF-α the melanoma cells switch to an equilibrium with a high concentration of the differentiated phenotype.

Conclusion: The simulations show that the model covers the behaviors reported in [5].
The next goal is to test new therapy protocols by simulations

Simulations: Therapy with T-cells with 2 different specificities

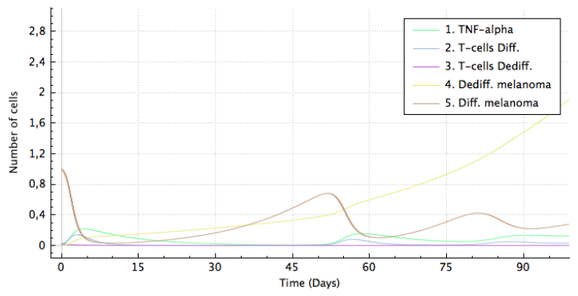


Figure 6: Dedifferentiated Relapse

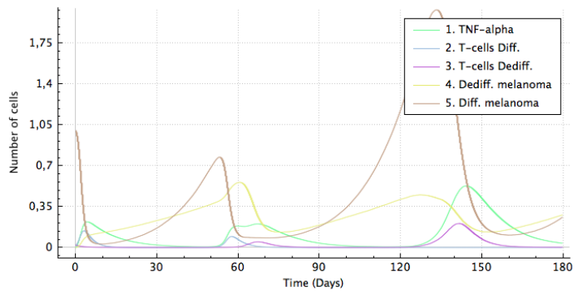


Figure 7: Finite cycle

In Figure 6 the T-cells attacking the dedifferentiated melanoma cells die out. The other T-cells still produce TNF-α and keep the population of differentiated melanoma cells small. In Figure 7 the T-cells attacking the differentiated melanoma cells die out. TNF-α still causes a switch to dedifferentiated melanoma cells which are kept small by the other T-cells. Thus, the whole system remains in a finite cycle.

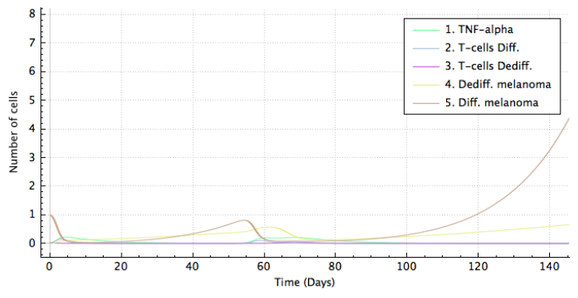


Figure 8: T-cells die out

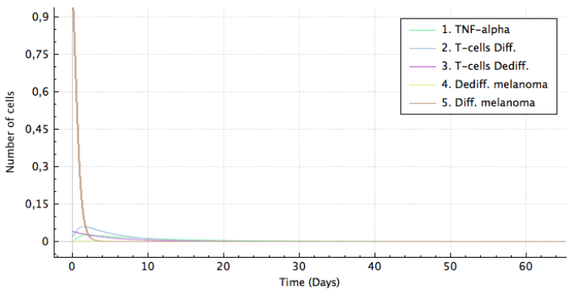


Figure 9: Tumor dies out

In Figure 8 both T-cell populations die out and a mixed relapse with a high proportion of differentiated melanoma cells occurs. In Figure 9 the simultaneous attack of the T-cells could completely eradicate the tumor. The cells which switched to the dedifferentiated phenotype could not survive as they do in Figure 1.

References

1. A. Bovier and S.-D. Wang. Trait Substitution Trees on Two Time Scales Analysis, *Markov Processes and Related Fields* , 19:607-642, 2013.
2. N. Champagnat and S. Méléard. Polymorphic evolution sequence and evolutionary branching. *Probab. Theory Related Fields*, 151(1-2):45-94, 2011.
3. N. Fournier and S. Méléard. A microscopic probabilistic description of a locally regulated population and macroscopic approximations. *Ann. Appl. Probab.*, 14(4):1880-1919, 2004.
4. M. Hölzel, A. Bovier, and T. Tüting, Plasticity of tumor and immune cells: a source of heterogeneity and a cause for therapy resistance? *Nat Rev Cancer*, 13(5): 365-376, 2013.
5. J. Landsberg *et al.* Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation. *Nature*, 490:1476-4687, 2012.