Third semester report

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1 Introduction

In the previous semester, we begin the inspection of the parameter space for the two compartment model. We were able to produce simulations that mimic some landmarks of CML progression. Despite this achievement, we still did not find out the fitting parameters for the appropriate description of CML progression.

2 Research work

In this semester, we deduced the correct function for the leaking. After many trials, we identify the logarithmic function is appropriate to reproduce the migration of blast cells to the blood compartment. The current expression for this function is $\lambda_k(t) = \beta \log(C(t)+1)\left(\frac{1}{\alpha^{N-k}}\right)$, where $C(t)$ is the total number of cells present in the bone marrow at time t and two free parameters α and β. In the process of describing the different phases of CML, we discover the lifetime of progenitor's cells in the blood compartment should be larger than the homeostatic turnover present in the bone marrow. Including these changes, we can produce the proper histogram of CP duration. It is possible to plot the histogram of blast percentage in the blood when cells with the critical number of mutations appear. The ongoing results from the model are consistent with the conceptual understanding of CML progression, depicted in figure 1.

The model can predict not only the CP duration but also the AP duration. The latent time, from the insertion of the leukemic stem cell to the detection of CML, is predicted from the simulations. These estimates are novel features from our model, and to the best of our knowledge, not previously investigated. There is possible to extract other useful information, for instance, the relation between the WBC and the percentage of blast cells in the bloodstream.

In the second part of this semester, we introduced resistant mutations as a new type of cells in the population. Resistant mutations can arise from leukemic cells with a rate of mutation μ_r, these cells don't possess any advantage compared with the sensitive mutations, in the absence of the treatment. Sensitive and resistance cells do not compete with each other in a direct way however, both types contribute to the leaking process. In the presence of the treatment, we introduced a negative mutation to the sensitive cells. The mutation is negative in the sense that it decreases the symmetric division rate and increases the differentiation, as opposed to positive mutations. This negative mutation is strong enough to reduce the symmetric division rate of leukemic cells to a value smaller than in the homeostatic regime, thus introducing apoptosis.

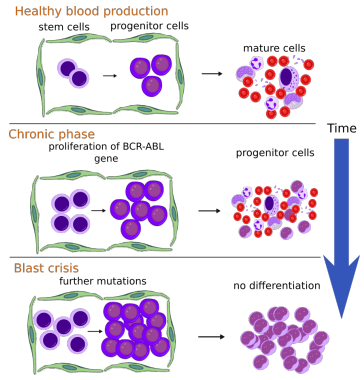

Figure 1: Conceptual progression of CML, with the representation of the two compartment model

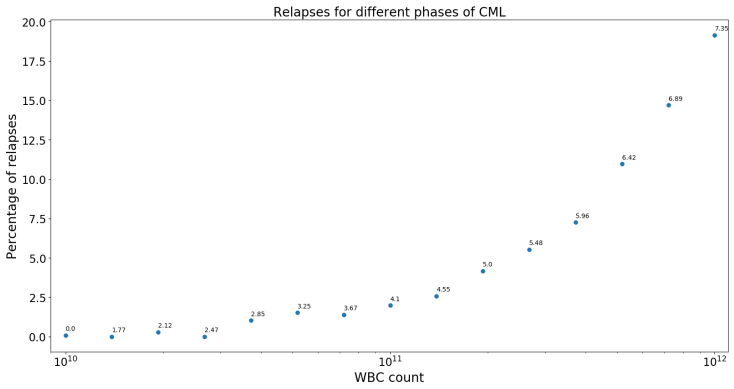

Figure 2: Percentage of relapses due to resistant mutations and mean blast percentage

We simulated leukemic relapse during treatment due to point mutations in the BCR-ABL gene. We computed the percentage of patients that achieved MCyR or CCyR, then relapse due to resistance mutations. This percentage will be increasing with respect to the begging of the treatment as it can be seen in figure 2. This result is consistent with the hypothesis that resistance cells are present prior treatment, implying there is no de novo resistance. We are running the simulations with different strength of the negative mutation representing the treatment, to explore the possibility of acquired resistance. We will investigate the possibility of replacing the leaking function by a leaking constant as part of the final analysis before concluding this project.

3 Attended courses

- Phase transitions
- Preclinical models in cancer
- Macromolecules
- Machine Learning

4 Conferences

I didn't attend any conferences in this semester

References

[1] Franziska Michor, Timothy P. Hughes, Yoh Iwasa, Susan Branford, Neil P. Shah, Charles L. Sawyers & Martin A. Nowak. Nature, 435 12671270 (2005).